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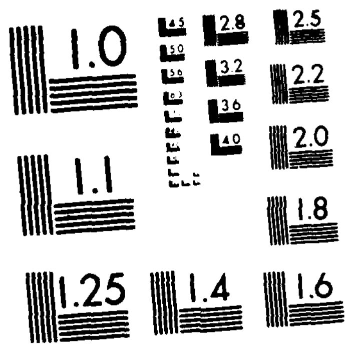

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MOLECULAR MODELING IN DRUG DESIGN FOR THE DEVELOPMENT OF ORGANOPHOSPHORUS ANTIDOTES/PROPHYLACTICS

ANNUAL REPORT

August 1985
(For the period June 1, 1984 - May 31, 1985)

Dr. Tamara Gund

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

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New Jersey Institute of Technology
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FOREWORD

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I. STATEMENT OF PROBLEM UNDER STUDY

We are interested in studying the muscarinic acetylcholine receptor. Our work will involve molecular modeling of muscarinic agonists and antagonists to determine their bioactive conformations. From the modeled ligands we hope to derive a pharmacophoric pattern common to the ligands. This pharamcophoric pattern will enable a topography of the muscarinic receptor to be derived which will facilitate the design of novel agonists and antagonists. The work will concentrate on the design of new antagonists which could be synthesized and tested by army collaborators. These antagonists we hope will prove to be new antidotes for organophosphate poisons. [illegible] molecular structure, molecule molecule interactions, synthesis (chemistry), computer programs

II. BACKGROUND AND REVIEW OF LITERATURE

The malfunctioning of acetylcholine mediated transmission of nervous signals (which involves nicotinic and muscarinic receptors as well as acetylcholinesterase enzyme) is responsible for many diseases incurred by man[1], and interfering with cholinergic transmission is a key strategy in chemical warfare.[1c] Many nerve poisons function by inhibiting acetylcholinesterase, which prevents removal of released neurotransmitter, resulting in overstimulation of the cholinergic receptors. This produces biological responses that eventually may cause death.

An antidote may reverse the effects of acetylcholinesterase inhibitors by either binding to the receptor to reduce overstimulation by the agonist, or by reacting with the inhibitor, thereby reactivating the acetylcholinesterase enzyme

so that it can resume its original function.[1c]

The acetylcholine receptor (AChR) is representative of a large class of membrane proteins responsible for the electrical activity of the nervous system. The receptor upon binding of an agonist responds by opening a channel and allowing ions to pass through the membrane. The ion flows produce electrical signals which cause nerve impulve activity, such as muscle contraction.

An agonist combines with the acetylcholine receptor to initiate changes in conformation states that results in the opening of the ion channel. The mechanism by which this process occurs is still unknown. The agonist is believed to remain bound to the receptor during activation, thus suggesting that the acetylcholine receptor can mold its conformation to fit the agonist structure.[2e] One method of studying the binding process is by structure-activity relationships. This endeavor is however difficult because most agonsits are flexible molecules and their bioactive conformations are undetermined. Rigid agonists facilitate the solution of this problem since the number of possible conformations is greatly diminished. The number of possible complementary conformational states of the receptor is likewise reduced.

Both the nicotinic and muscarinic receptors have been thoroughly studied,[2] although much more is known about the nicotinic system. The nicotinic receptor has been isolated from membranes, and reconstituted back into the membrane environment.[2f] The muscarinic receptor has not been isolated in pure form, because a convenient source which contains large amounts of the receptor has not yet been found.[3]

Since the actual structure of neither receptor is known, indirect methods have been used to gain insight into the structure, the binding mechanism, the geometry of the receptor site, and the bound conformations of agonists and antagonists.

Nonrigid molecules possess functional groups that are free to adopt a large number of spatial orientations. Predictions of the most probable conformers of these flexible molecules can be made either empirically, e.g. x-ray, NMR spectroscopy, 1R, etc., or theoretically, via calculations.[4] The assumption is often made that the preferred conformations are those that are most likely to be the active form of the molecule.[5] Molecules that have the same pharmacological effects are considered, and their conformational profiles compared for structural similarities.

The conformations of acetylcholine and other cholinegic ligands have been studied experimentally and computationally by many workers.[2,6,7] The types of calculations performed include Extended Huckel Theory (EHT), Intermediate Neglect of Differential Overlap (INDO), Perturbative Configuration Interaction of Localized Orbitals (PCILO), and ab initio calculations at the STO-3G level. Most of the calculations involved flexible molecules, and centered around deriving energy surfaces of fixed conformations with varying torsional angles of interest.[6]

Two receptor models for nicotinic and muscarinic binding were derived. One by Kier[7], shown in figure 1, is based upon comparisons of interatomic distances separating atomic centers of functional importance. The other, by Chothia and Pauling[3]

(figure 2), is based on preferred values of relevant dihedral angles from x-ray crystallographic studies of potent cholinomimetics.[9]

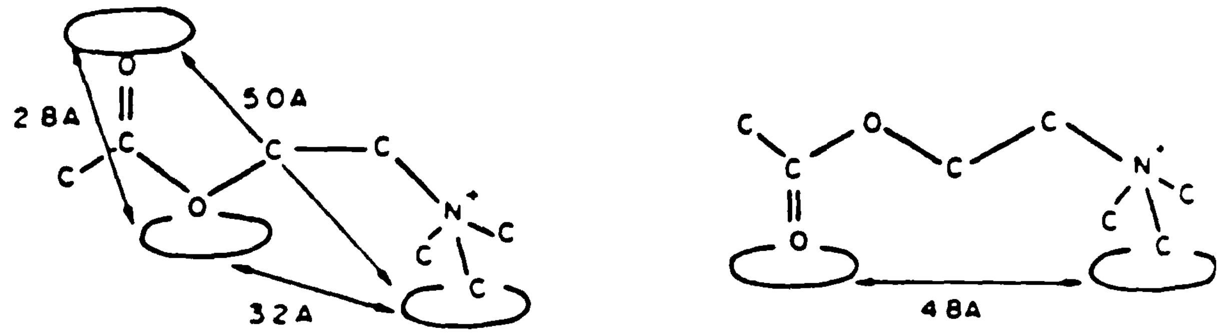


Fig. 1 The cholinergic receptor models of Kier showing the interaction of the preferred conformers of acetylcholine with (a) the muscarinic receptor and (b) the nicotinic receptor

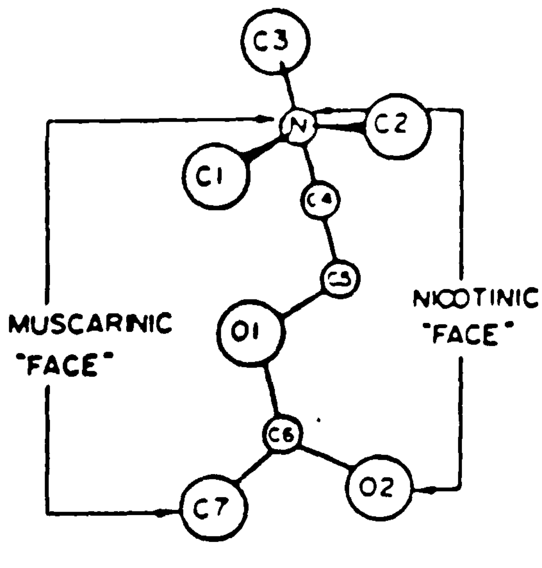


Fig 2. The Chothia-Pauling cholinergic model indicating the "nicotinic face" which consists of the quaternary nitrogen and carbonyl oxygen and the "muscarinic face" which is the quaternary nitrogen and acetyl methyl group.

Both models are based on fixed conformations of agonists and antagonists bound to the receptors, and both proposals fail to explain the activity of the reverse ester of acetylcholine. Donelsmith et al[4] found it necessary to invoke a model based on flexible receptors and ligands.

Schulman, Sabio and Disch[10] derived a preferred muscarinic pharmacophore (figure 3) by calculation of conformational energies and energies of interaction to a hypothetical carboxylate group (CO_2) for a coloumbic interaction and to an OH for a similar hydrogen bonding interaction. Their pharmacophoric pattern incorporates the distances between the receptor carboxylate (P) and hydroxy (Q) and the angle between them. This pharmacophore corresponds to an angle PNOQ between 60 and 117°. This pharmacophore does not however explain the binding of all the muscarinic agonists.

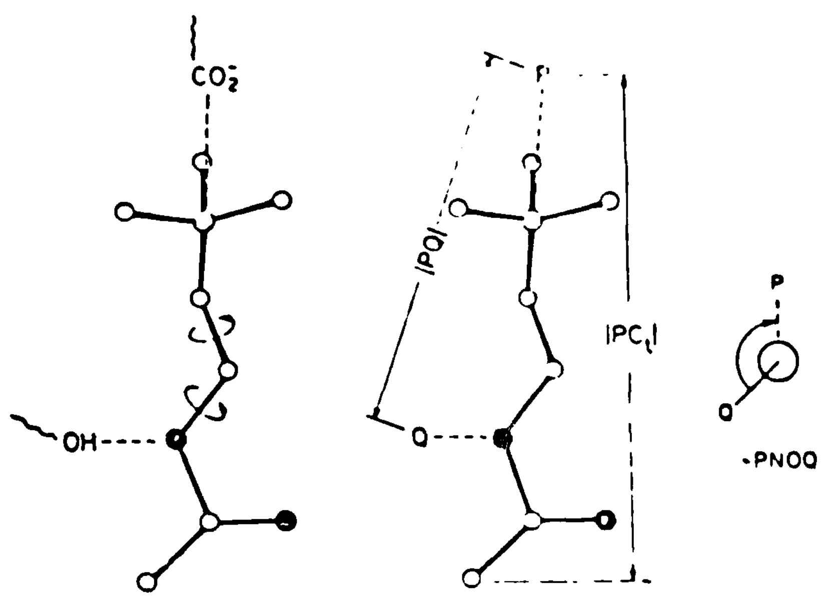


Figure 3 (a) Acetylcholine interacting with the receptor's carboxylate oxygen and an electrophilic group, such as a hydrogen-bonding proton. (b) The oxygen is indicated symbolically by *P* while the electrophilic site is located at the point of minimum electrostatic potential near the ester oxygen, denoted by *Q*. The interaction dihedral angle *PNOQ* is indicated on the right-hand side of the figure. Also shown are the distances $|PQ|$ and $|PC_t|$.

Beers and Reich[11] proposed a pharmacophoric distance for active muscarinic and nicotinic agonists. They predicted that the optimal distance between the site of coulombic interaction (quaternary nitrogen) and hydrogen bonding interaction (ester oxygen) for a muscarinic agonist is 4.44A.

Pullman , Courriere and Coubeils[12] performed quantum mechanical studies (PCILO) on acetylcholine, nicotine and muscarine to determine their conformational and electronic properties. Their conformational studies agreed with experimental data and their electronic studies revealed that the nitrogen on acetylcholine is almost neutral and the positive chargesare spread over the three methyl groups, thus forming a large positive area for coulombic interaction with the receptor. Pauling[8] performed calculations on a series of anticholinergic substances, and discovered a consistent low energy conformation in all but two compounds, and determined which functional groups were necessary for pharmacological activity. The calculated energy of the consistent conformation was generally less than the crystal conformations, and for the two remaining structures the consistent conformations were only 2 kcal higher than the crystal structures. Weinstein[13] performed quantum mechanical calculations on 3-acetoxyquinuclidine and found that the molecule could adopt the gauche acetylcholine binding conformation. The interaction pharmacophore of the active species was defined by the electrostatic potential fields which were generated, and revealed a reactivity pattern identical with acetylcholine.

The structures of many agonists and antagonists of acetylcholine receptors are known. Activity and specificity varies with conformation and configuration of the molecule. A systematic computer graphic study of semirigid receptor agonists and antagonists could assist in correlating the structures of these drugs to their actions. Computer calculations now enable accurate predictions of preferred conformations[14], charge densitites, electrostatic potential contours and pharmacophoric patterns[15,16]. Without computers it is difficult to superimpose three dimensional molecular models to see how well two or more structures conform to one another, or to search for common structural elements. Also with models one can only guess at preferred conformations and relative energies, at charge densitites and electrostatic potential contours.

III. OVERALL PLAN

The overall strategy for studying the muscarine receptor and designing of antagonists which could serve as antidotes for nerve gas poisons is outlined below:

A. Obtain State of the Art Systems for Modeling Muscarinic Ligands and for Receptor Mapping

   1. Hardware

      a. Graphics

      b. Computer

   2. Software

      a. Graphics - Input, Display

      b. Calculations

B. Assemble a Project Team

C. Collect Suitable Muscarinic Ligands and Reliable Biological Data From the Literature

D. Establish a Viable Collaboration to Obtain New Compounds and Biological Data

E. Investigate Various Modeling Techniques for Applicability to the Research Problem

F. Apply Appropriate Techniques to Modeling Molecules of Interest

G. Draw Conclusions Related to Design of Muscarinic Antagonists

H. Derive a Geometric Model for the Muscarinic Receptor Site

I. Design Novel Muscarinic Antagonists for Synthesis and Pharmacological Testing

In the first year of this contract we have made substantial progress on objectives A, B, C, D, E, F, and G, as detailed in the remainder of this report.

IV. PROGRESS TO DATE

A. HARDWARE

The hardware that has been acquired for this project includes an Evans and Sutherland PS 330 Color Vector Terminal and two Advanced Electronics Design (AED) 767 color raster terminals, all interfaced to a VAX 11/780 super minicomputer.

B. SOFTWARE

At the start of this project the TRIBBLE[17] software from Dupont was available. At that time we were going to build a modeling system based on TRIBBLE, and use it for studying muscarinic agonists, antagonists and for receptor mapping. But

since then, there has been an explosion of modeling software on the commercial market, and so we dispensed for the time being withthe idea of developing a software system and proceeded to acquire available modeling systems through grants andpurchasing. The following systems are now in-house and are being used for this project: (1) TRIBBLE from D. Pensak, Dupont de Nemours; (2) CHEMGRAF, from Keith Davies, Chemical Design Ltd, Botley works, Oxford, England; (3) CHEMLAB, from Molecular Design Ltd., San Leandro, California; and (4) SYBYL, from TRIPOS, St. Louis, Missouri. TRIBBLE was obtained at no charge; CHEMGRAF and CHEMLAB were acquired through other grants, but updates will be obtained through this contract. SYBYL was awarded as a grant from TRIPOS; the first year's maintenance fee was paid by the university.

Our objective for obtaining these various modeling packages was to explore different modeling techniques in order to use optimal methods for modeling muscarinic ligands and mapping their receptor. In our experience, no single software package is adequate for solving this problem. Various portions of each package are superior to the others, and addition of programs, parameters and interfaces are still necessary.

Besides the above modeling packages, other calculational programs have been obtained and interfaced. These include QuantumMechanical Methods:MOPAC (MNDO,MINDO) from M.J.S. Dewar (available through QCPE), Gaussian 82 from J. Pople (available from QCPE), PRDDO obtained from T. Halgren (Merck, Sharpe & Dohme); and a Classical mechanical method:,MM2, from Allinger (available from QCPE).

C. PERSONNEL

Much time during this period was taken up in assembling a first rate project team. Team members include a systems programmer, Dr. Rong Fa Liang, who is responsible for all software and hardware developments and maintenance; a postdoctoral fellow, Dr. Mark Hermsmeier, who will join the group August 1, 1985 and will be responsible for all applications work; and myself. A consultant, Kai Wen Jen, has been used for some specialized software development.

D. ACCOMPLISHMENTS

1. Interfacing of Programs

CHEMGRAF, TRIBBLE, and MOPAC have been interfaced so that data can be generated in one program and used in another.

We typically use TRIBBLE modules for structure generation and calculation. Data are then read into CHEMGRAF for display and other manipulations. The following modifications in TRIBBLE and CHEMGRAF have been performed.

a. TRIBBLE mimized (MM2) structures (TRIBBLE CONFILE) can be viewed and modified in CHEMGRAF ("modify/cursor") and sent back to TRIBBLE for MM2 minimization. The process can be repeated as often as one likes. The reason for this modification is that CHEMGRAF minimizations are not as rigorous as the calculations in TRIBBLE, but the graphics input, display and modification features in CHEMGRAF are superior to those in TRIBBLE.

b. CHEMGRAF sketched structures can be converted to TRIBBLE recognized files (TRIBBLE CON). These can then be sent for MM2 calculations and the optimized structures viewed by CHEMGRAF. One problem encountered in interfacing different molecular modeling systems is that whenever an operation is performed, such as sketching of a structure using the graphics programs, a file of data is created which must be in the correct format for recognition by the next program. Different modeling systems use different file formats.

c. TRIBBLE, MOPAC and CHEMGRAF have been interfaced so that graphics of CHEMGRAF, molecular mechanics (MM2) and Semi-empirical calculations (CNDO) of TRIBBLE, and MNDO and MINDO of MOPAC can be utilized and data sent back and forth automatically. The procedure involves generating a CON file in TRIBBLE, converting this to a TRE file which can then be submitted to a CNDO calculation in TRIBBLE or sent to MOPAC for a better MNDO or MINDO calculation. The MOPAC charge files or CNDO charge files can then be read into the CHEMGRAF electrostatics program for generation of an electrostatic surface. Programming was done to convert TRIBBLE TRE files to MOPAC input formats.

2. **Parameterization of Allingers MM2 program.**

The normal version of MM2 does not handle charges properly and was not parameterized for ammonium salts. Since all the molecules that we are presently considering are ammonium salts, MM2 was modified for us to handle charges by Dr. T. Halgren of Merck Sharpe and Dohme. Parameters were developed in conjunction with Dr. J. Snyder, presently of Searle. Parameters were developed from x-ray data on cyclic and non-cyclic ammonium

salts and futher refined by calculations at the 6-31G* level. We had to alter the normal MM2 program within TRIBBLE to incorporate these changes.

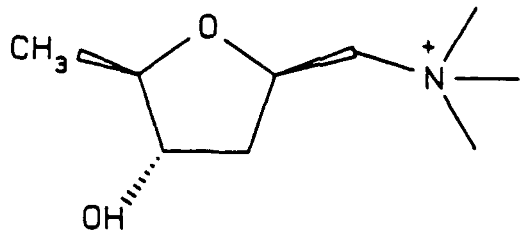
3. Muscarinic Agonists Modeled

Chart I lists the agonists that were modelled using TRIBBLE for structure input; CHEMGRAF for display and manipulation; molecular mechanics (MM2 revised version with ammonium salt parameters) for calculation of minimum energy conformations;

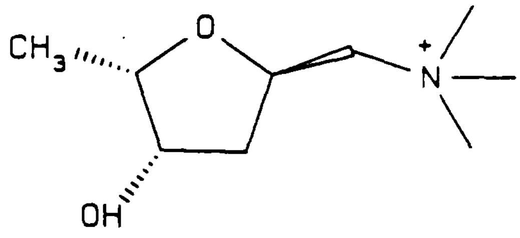
MOPAC (MNDO) for charge calculations; and CHEMGRAF for electrostatic potential energy contours.

CHART I

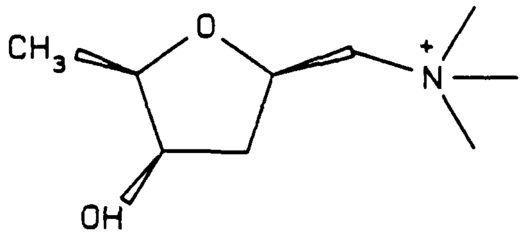
AGONISTS THAT WERE MODELLED USING TRIBBLE FOR STRUCTURE INPUT



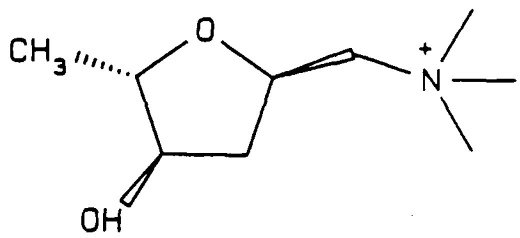
a. muscarine



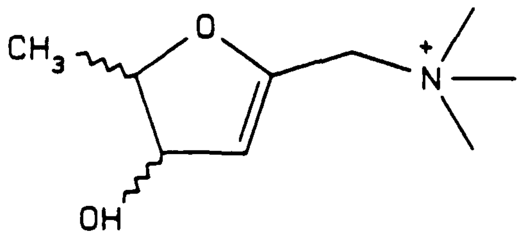
b. epiallomuscarine



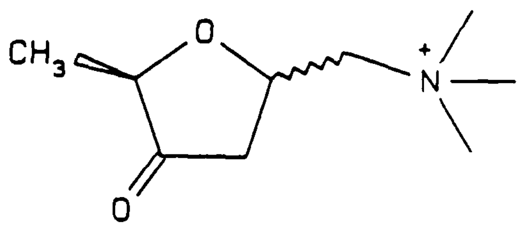
c. epimuscarine



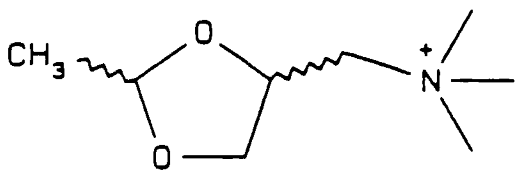
d. allomuscarine



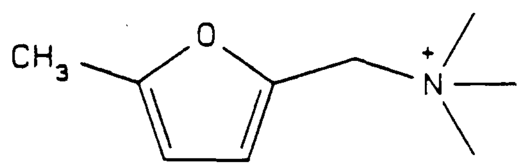
e. cis/trans 2,3 dehydromuscarine



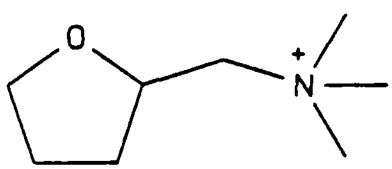
f. cis/trans Muscarone



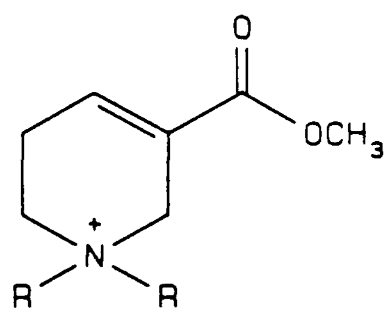
g. cis/trans F2268



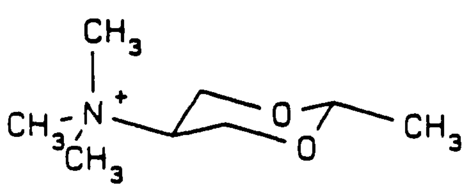
h. 5-methylfurmethide



i. TFTM



j. arecoline



k. F2581

4. **Molecular Modeling Approach Used**

Biological activity is a result of ligand-receptor binding. It is well known that drug - receptor interactions are analogous to a lock and key concept where complementarity is needed to involve a biological response. However, drug - receptor interactions are governed by electrostatic attractions, as well as geometric factors. We therefore, have calculated conformational and electronic properties of the agonists in Chart I. Our approach involved (a) generating three dimensional structures from two dimensional sketches, (b) calculating minimum energyconformations by the revised MM2 program; (c) identifying the pharmacophoric pattern; (d) comparing structures according to steric energies and physical parameters, bond lengths, bond angles, and non-bonding distances; (e) calculating partial atomic charges using MNDO (MOPAC); (f) calculating electrostatic potential energy contour surfaces.

5. **Optimization Studies**

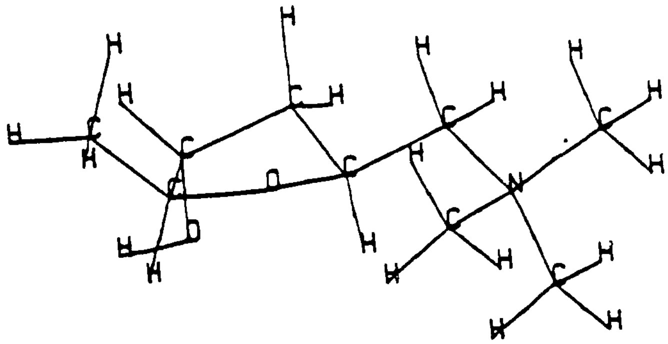
Chart II gives structures for the lowest energy conformers of the agonists in Chart I.

Beers and Reich[11] and others[5] have proposed that for the muscarine analogs, the major sites of interaction between the agonist and the receptor involve a coulombic and a hydrogen bonding interaction involving the quaternary nitrogen and the ring oxygen, respectively. Beers and Reich[11] proposed that the distance between the coulombic and the hydrogen bonding interaction (at the van der Waals extension of the ring oxygen) should be 4.44A°. We therefore calculated the distances between

CHART II

GLOBAL MINIMUM STRUCTURES

a. Muscarine



b. Epiallomuscarine

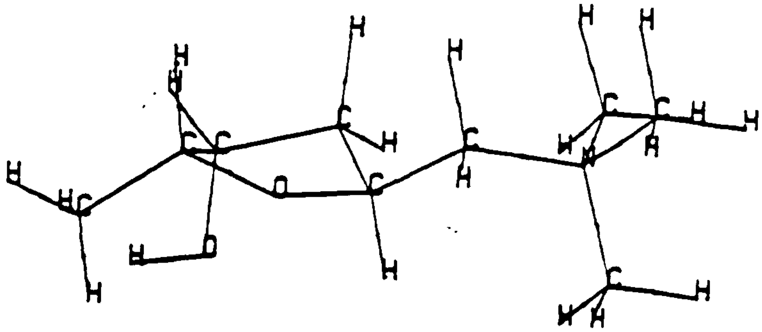
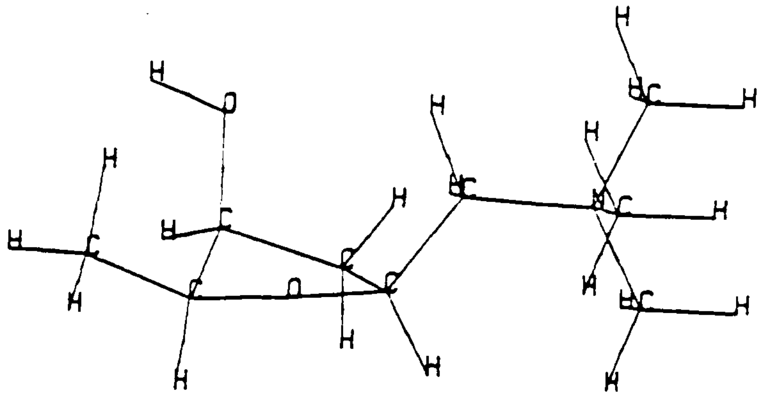


CHART II

GLOBAL MINIMUM STRUCTURES

c. Epimuscarine



d. Allomuscarine

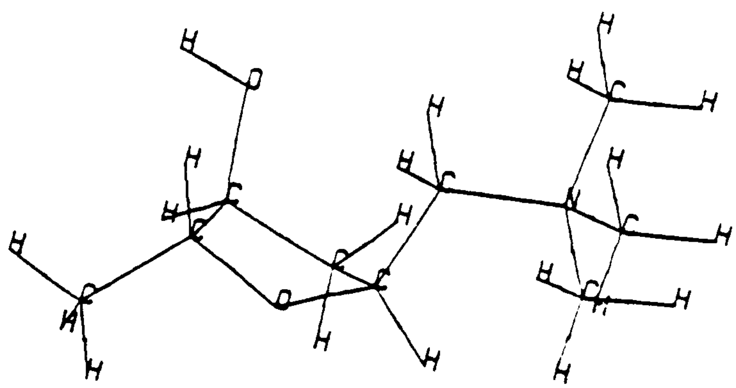
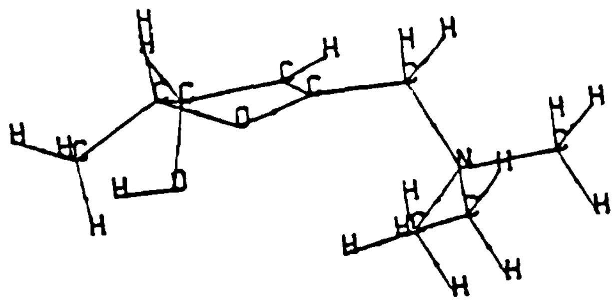


CHART II

GLOBAL MINIMUM STRUCTURES

e. Dehydromuscarine (2,3)(cis)



f. Dehydromuscarine (2,3)(trans)

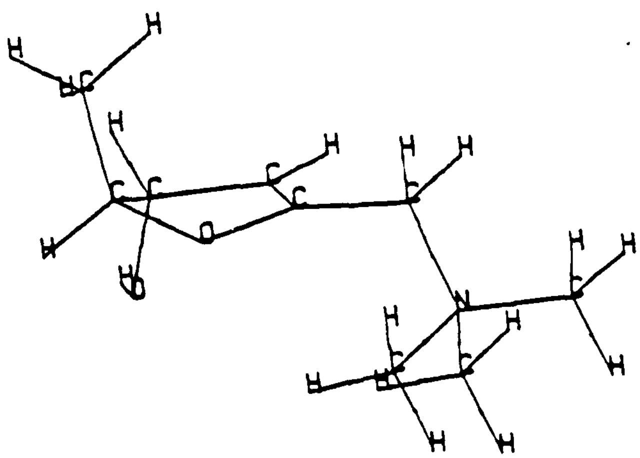
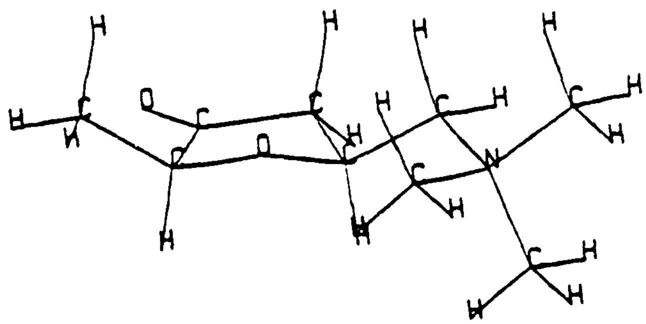


CHART II

GLOBAL MINIMUM STRUCTURES

g. Muscarone (cis)



h. Muscarone (trans)

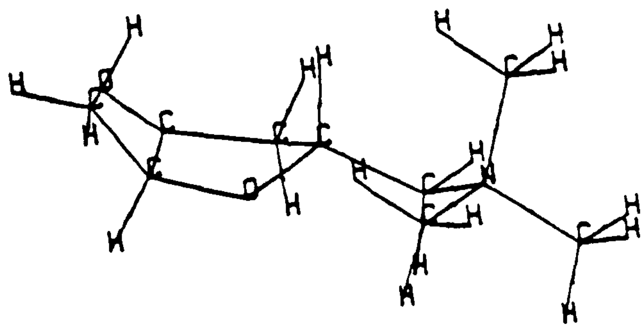
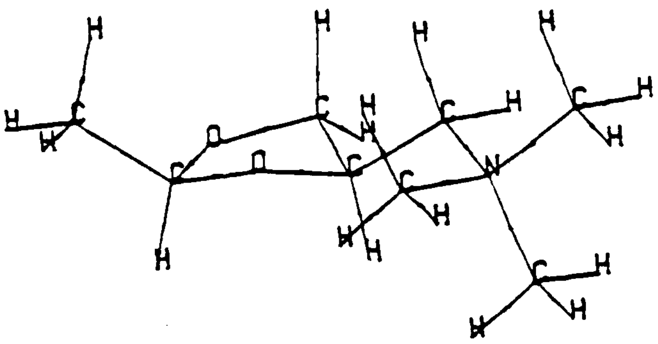


CHART II

GLOBAL MINIMUM STRUCTURES

i. F 2268 (cis)



j. F 2268 (trans)

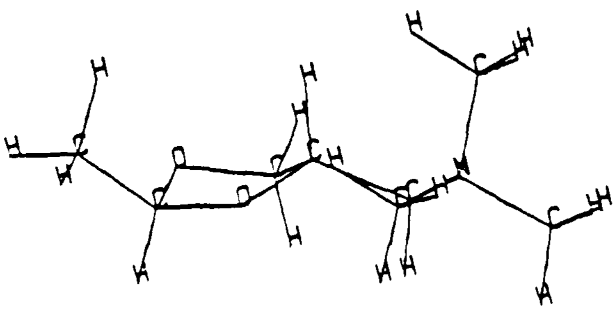
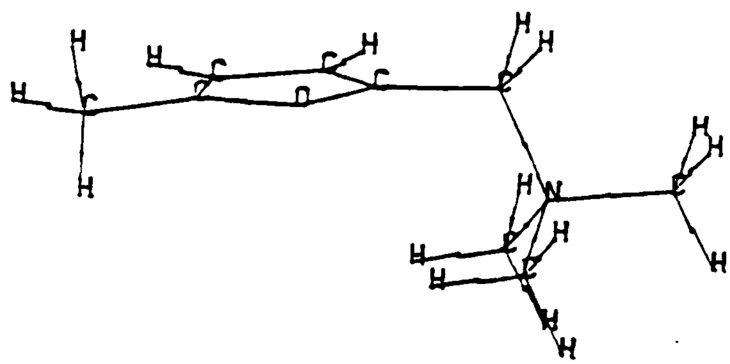


CHART II

GLOBAL MINIMUM STRUCTURES

k. 5-Methylfurmethide



1. TFTM

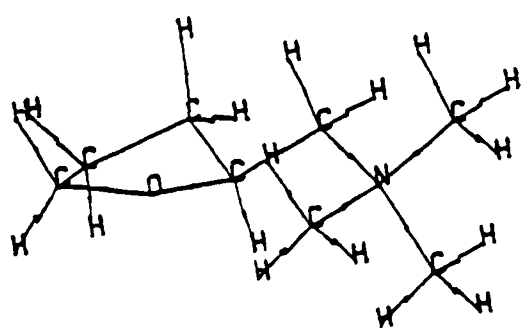
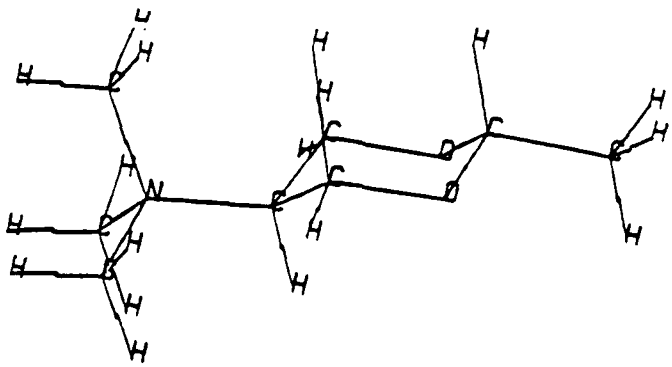


CHART II

GLOBAL MINIMUM STRUCTURES

m. F 2581



n. Arecoline (H,H)

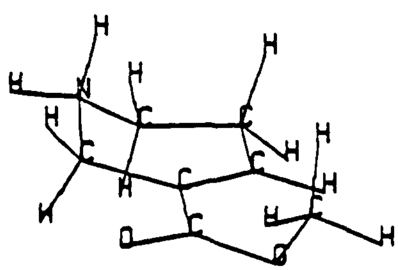
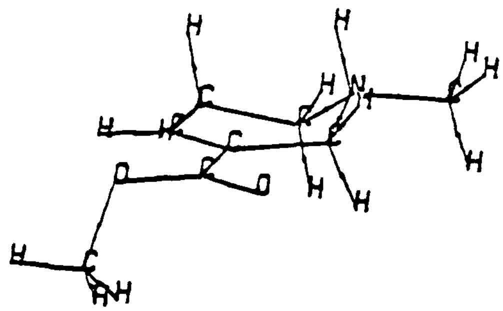


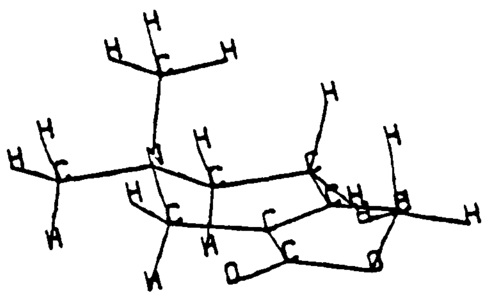
CHART II

GLOBAL MINIMUM STRUCTURES

o. Arecoline (H, CH_3)

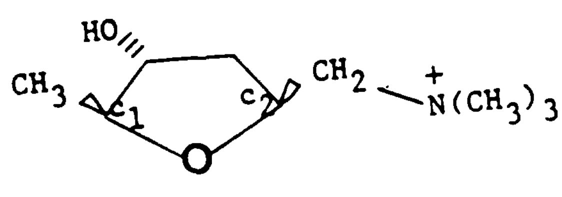


p. Arecoline (CH_3,CH_3)



the quaternary nitrogen and ring oxygen extension for the minimum energy structures which were generated. Table I lists the steric energies, extended N...0 distances, and dihedral angles of the side chains for the lowest energy structures. As can be seen, the Beers and Reich distance of 4.44A^{o} is not achieved in the lowest energy conformers which have extended N110 distances of about 3.0A^{o}. We therefore searched for other low energy conformations. Where a rotatable side chain is present we used the MM2 dihedral driver option to generate conformations with 30^{o} incremental rotations over a 360^{o} range. Tables II-XVII indicate the correlation of dihedral angle with steric energy and extended N...O distance. In all cases several conformations with the critical distance around 4.4A^{o} are possible. The conformations most likely to be important for bioactivity are those within 5 kcal of the global minimum[10]. These are indicated in the Tables. The smaller the energy difference between the global minimum and the possible bioactive conformation the more likely that the conformation can be achieved.

The procedure that we used to calculate the nonbonding distances between O....N at the Van der Waals extension of oxygen is illustrated for muscarine and is as follows:



Muscarine

Table I

MM2 Calculated - Global Minimum Structures

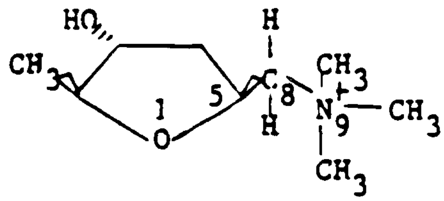
Agonist	[a]Steric Energy	Degree of Dihedral Angle 1,5,8,9	[b]Non-Bonded Dist. Between N···O (A°)
Muscarine	27.71	73.25	3.064
Epiallomuscarine	27.90	70.00	3.046
Epimuscarine	27.31	65	2.998
Allomuscarine	28.49	65	3.047
Dehydromuscarine(cis)	12.89	75.35	3.527
Dehydromuscarine (trans)	13.29	69.46	3.415
Muscarone(cis)	31.14	72.25	3.125
Muscarone(trans)	31.85	-72.82	3.108
F2268(cis)	22.61	70.35	3.115
F2268(trans)	22.68	-73.18	3.133
5-methylfurmethide	4.94	72.3	3.589
TFTM	25.74	71.38	3.047
F2581	33.08	diequatorial	5.13
Arecoline (H,H)	-15.13	180	5.761
Arecoline (H, CH_3)	-13.05	180	5.621
Arecoline (CH_3,CH_3)	- 8.09	180	5.823

[a]Units - kilocalories/mole

[b]N...O - distances calculated by adding 1.74Å to the ether oxygen by the method described in the text.

TABLE II - Muscarine-

MM2 Calculations Dihedral Angle vs Steric Energy and Non-Bonding Distance

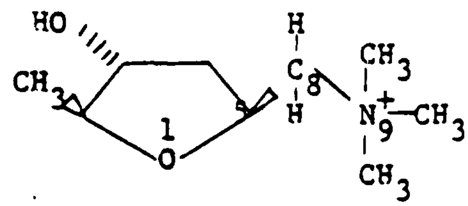


Degree of Dihedral Angle 1-5-8-9	Steric Energy	Non-Bonded Dist. Betw. $\overset{+}{N}$&O (without adding 1.74)	Non-Bonded Dist. Betw. $\overset{+}{N}$&O (adding 1.74)
0^o	32.0992	2.881	2.589
30^o	30.1730	2.928	2.625
60^o	27.9962	3.082	2.931
90^o	28.4646	3.294	3.384
120^o	30.6470	3.561	3.921
*150^o	30.0632	3.745	4.291
*180^o	30.3956	3.801	4.405
210^o	37.9842	3.738	4.358
240^o	51.0647	3.561	4.096
270^o	36.3006	3.314	3.501
300^o	37.119	3.037	2.943
330^o	-	-	-
360^o	32.1006	2.882	2.588
**73.25^o	27.71	3.144	3.064 Global Minimum

*Beers and Reich distance can be achieved within a resonable (< 5kcal) energy difference from the global minimum.

TABLE III - Epiallo muscarine

MM2 Calculations Dihedral Angle versus Steric Energy and N....O Nonbonded Distance

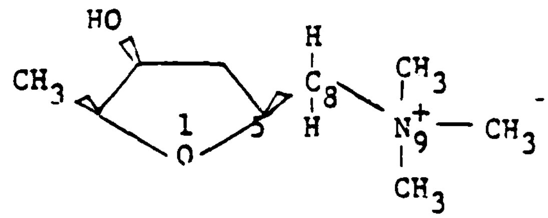


Angle	Steric Energy	Non-Bonded Dist. Betw. $\overset{+}{N}$&O	Adding 1.74
0^o	32.5077	2.887	2.754
30^o	30.2524	2.936	2.717
60^o	28.1305	3.086	2.928
90^o	28.7245	3.296	3.349
120^o	30.8554	3.564	3.899
*150^o	30.2598	3.744	4.278
*180^o	30.5754	3.806	4.477
210	40.5153	3.743	4.496
240	49.8966	3.566	4.298
270	35.1314	3.305	3.610
300	36.1160	3.026	3.052
330	-	-	-
360	32.5109	2.889	2.700
70^o	27.8961	3.145	3.046 -Global Minimum

*Beers and Reich distance can be achieved within a reasonable (0.5kcal.) energy difference from the global minimum.

TABLE IV - Epimuscarine MM_2 Calculations

Dihedral Angle Versus Steric Energy and Nonbonded N···O Distance

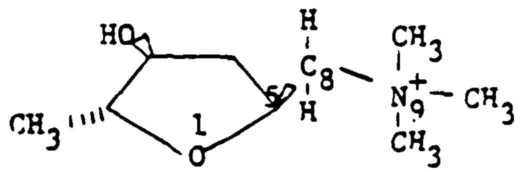


Angle	Steric Energy	Non-Bonded Dist. Betw. $\overset{+}{N}$&O	Adding 1.74
0^{o}	31.47	2.877	2.800
30^{o}	28.9260	2.910	2.798
60^{o}	27.3719	3.055	2.947
90^{o}	28.4111	3.266	3.369
120^{o}	30.4002	3.542	3.937
*150^{o}	29.5390	3.729	4.315
*180^{o}	31.0881	3.806	4.426
210^{o}	54.6888	3.744	4.382
240^{o}	57.0296	3.568	4.124
270^{o}	37.8808	3.293	3.538
300^{o}	36.2178	3.015	2.986
330^{o}	42.1248	2.790	2.472
360^{o}	31.3326	2.869	2.695
** 65^{o}	27.3140	3.084	2.998 - Global Minimum

*Beers and Reich distance can be achieved within a reasonable (5kcal) energy difference from the global minimum.

TABLE V - Allomuscarine MM2 Calculations

Dihedral Angle Versus Steric Energy and N····O Nonbonded Distance



Angle	Steric Energy	Dist. (without adding 1.74	Adding 1.74
0^{o}	33.0342	2.896	3.053
30^{o}	30.0768	2.916	2.949
60^{o}	28.4934	3.059	3.025
90^{o}	29.0921	3.285	3.632
*120^{o}	31.1177	3.556	4.136
*150^{o}	30.7894	3.739	4.526
*180^{o}	32.7963	3.812	4.812
210^{o}	44.5254	3.751	4.916
240^{o}	-	-	-
270^{o}	51.3878	3.625	4.852
300^{o}	54.4142	3.413	4.481
330^{o}	-	-	-
360^{o}	32.5591	2.868	2.743
** 65^{o}	28.4932	3.088	3.047 (Global Minimum

* Beers and Reich distance can be achieved within a reasonable (<5kcal.) energy difference from the global minimum.

TABLE VI

DEHYDRO-MUSCARINE (CIS) - DIHEDRAL DRIVER CALCULATIONS

ANGLE	STERIC ENERGY	NON-BONDED BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	16.8362	3.011	2.982
30	15.3340	3.048	3.008
60	13.3445	3.175	3.301
90	13.8236	3.385	3.779
*120	17.2516	3.611	4.205
*150	19.0228	3.783	4.526
*180	18.9680	3.839	4.679
210	21.8192	3.784	4.642
240	19.5610	3.627	4.399
*270	14.9363	3.396	4.018
300	15.2707	3.162	3.500
330	-	-	-
360	16.6017	3.009	2.991
GLOBAL MINIMUM			
75.35	12.8871	3.269	3.527

*Beers and Reich N...O distance can be achieved within a reasonable energy difference from the global minimum.

TABLE VII

DEHYDRO-MUSCARINE (TRANS)- DIHEDRAL DRIVER CALCULATIONS

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	16.7992	3.011	3.030
30	15.4710	3.050	3.042
60	13.4395	3.177	3.302
90	13.6632	3.375	3.753
* 120	16.9415	3.610	4.195
* 150	18.6415	3.784	4.527
* 180	18.5633	3.838	4.677
210	21.3898	3.783	4.641
240	19.4275	3.626	4.399
270	14.7920	3.332	3.922
300	15.7969	3.079	3.379
330	-	-	-
360	16.5426	3.007	2.998
GLOBAL MINIMUM 69.46	13.2904	3.223	3.415

*Beers and Reich N...O distance can be achieved within a reasonable energy difference from the global minimum.

TABLE VIII

MUSCARONE(CIS) (DIHEDRAL ANGLE DRIVER CALCULATION)

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	35.4632	2.883	2.579
30	33.5596	2.938	2.648
60	31.3711	3.089	2.960
90	32.0099	3.304	3.414
*120	34.3315	3.570	3.945
*150	33.4717	3.750	4.304
*180	33.3810	3.813	4.431
210	46.5779	3.750	4.381
240	56.0390	3.573	4.116
270	39.4803	3.321	3.512
300	40.1041	3.045	2.956
330	-	-	-
360	35.4635	2.886	2.584
GLOBAL MINIMUM			
72.254	31.1444	3.166	3.125

*Beers and Reich N...O distance can be achieved within a resonable energy from the global minimum

TABLE IX

MUSCARONE(TRANS) (DIHEDRAL ANGLE DRIVER CALCULATION)

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	36.9340	2.866	2.590
30	35.9857	2.945	2.951
60	35.9474	3.127	3.578
90	39.4441	3.397	4.269
120	42.6102	3.654	4.858
150	39.0393	3.784	5.028
180	37.7577	3.826	4.941
210	39.2353	3.764	4.667
240	40.8118	3.589	4.271
270	38.3541	3.335	3.841
300	37.8082	3.061	3.497
330	55.1198	2.844	3.371
360	36.8031	2.876	2.597
GLOBAL MINIMUM			
-72.817	31.8475	3.171	3.108

TABLE X

F2268(CIS) (DIHEDRAL ANGLE DRIVER CALCULATION)

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	26.7321	2.882	2.657
30	25.1673	2.934	2.684
60	22.9113	3.085	2.984
90	23.3569	3.297	3.430
*120	25.8362	3.560	3.957
*150	25.2501	3.740	4.338
*180	25.0284	3.800	4.467
210	36.5119	3.737	4.429
240	52.2328	3.561	4.175
270	30.7114	3.288	3.542
300	31.5263	3.008	2.980
330	36.2617	2.782	2.480
360	26.7295	2.884	2.653
GLOBAL MINIMUM			
70.350	22.6097	3.146	3.115

*Beers and Reich distance can be achieved within a reasonable energy difference from the global minimum.

TABLE XI

F2268(TRANS) (DIHEDRAL ANGLE DRIVER CALCULATION)

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	27.0962	2.896	2.742
30	26.3905	2.954	3.035
60	27.8748	3.155	3.491
90	28.8113	3.374	3.847
120	31.9911	3.624	4.244
150	28.7478	3.770	4.439
*180	25.2976	3.803	4.484
*210	26.8101	3.739	4.273
240	27.5736	3.562	3.875
270	23.4769	3.296	3.395
300	24.5012	3.013	2.858
330	33.2217	2.788	2.506
360	27.1035	2.887	2.756
GLOBAL MINIMUM			
-73.183	22.6839	3.168	3.133

*Beers and Reich distance can be achieved within a reasonable energy difference from the global minimum.

TABLE XII

5-METHYLFURMETHIDE - DIHEDRAL ANGLE DRIVER CALCULATIONS

(O-C-C-N) ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)
0	7.8054	2.903
30	6.8470	3.042
60	5.2360	3.407
90	5.1620	3.868
*120	7.8222	4.288
*150	9.6616	4.555
*180	9.6294	4.634
*210	9.6615	4.554
*240	7.8221	4.287
270	5.1619	3.867
300	5.2378	3.407
330	6.8467	3.042
360	7.8052	2.901
GLOBAL MINIMUM		
72.3	4.9423	3.589

*Beers and Reich distance can be achieved within a reasonble energy difference from the global minimum.

TABLE XIII

TFTM - DIHEDRAL ANGLE DRIVER CALCULATIONS

(O-C-C-N) ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)
0	29.9969	2.673
30	28.0292	2.682
60	25.9540	2.911
90	26.5745	3.346
120	28.8811	3.893
* 150	28.3165	4.274
* 180	28.5027	4.455
210	31.9607	4.333
240	34.9764	4.214
270	31.4737	3.775
300	30.4913	3.488
330	29.1929	2.974
360	29.9960	3.047
GLOBAL MINIMUM		
71.38	25.7355	3.047

*Beers and Reich distance can be achieved within a reasonable energy difference from the global minimum.

TABLE XIV

F - 2581 - MM_2 Calculations

	STERIC ENERGY	NON-BONDED DIST. BETW. N^+ & O (ADDING 1.74)
E*	33.0837	5.131
A*	**	3.667

* E : EQUATORIAL, A : AXIAL expressed in bond $C\text{-}N^+$

** The conformer A is transformed to conformer E after minimization by MM2

TABLE XV

ARECOLINE (H, H) -DIHEDRAL ANGLE DRIVER CALCULATIONS

ANGLE(x)	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)	
* 0	- 7.3232	4.439	S-CIS
* 30	- 7.6732	4.455	
* 60	- 7.6363	4.641	
90	- 8.4700	4.805	
120	-11.6448	5.058	
150	-14.2788	5.404	
** 180	-15.1262	5.761	S-TRANS
210	-14.0699	6.041	
240	-10.8724	5.930	
270	- 7.1244	5.093	
300	- 6.6777	4.721	
330	- 6.9701	4.520	
360	- 7.3223	4.437	

** GLOBAL MINIMUM

*Beers and Reich distance can be achieved within a reasonable energy difference from the global minimum.

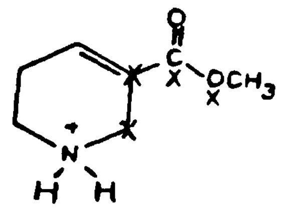


TABLE XVI

ARECOLINE (H, CH3) - DIHEDRAL ANGLE DRIVER CALCULATIONS

	ANGLE(x)	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)	
	0	- 5.2516	4.538	S-CIS
	30	- 5.1769	4.482	
	60	- 5.0884	4.471	
	90	- 5.7944	4.474	
	120	- 9.2410	4.689	
	150	-12.1585	5.138	
**	180	-13.0450	5.621	S-TRANS
	210	-12.0999	5.997	
	240	- 9.3215	6.026	
	270	- 5.9268	5.495	
	300	- 5.2402	5.051	
	330	- 5.3669	4.693	
	360	- 5.2513	4.540	

** GLOBAL MINIMUM

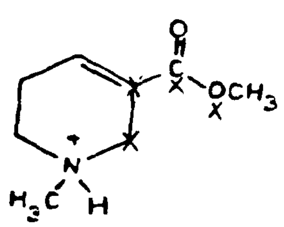
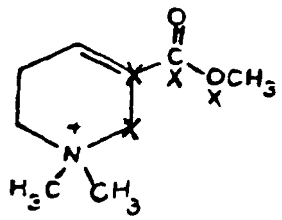


TABLE XVII

ARECOLINE (CH3, CH3) - DIHEDRAL ANGLE DRIVER CALCULATIONS

ANGLE(x)	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)	
0	-0.6485	4.452	S-CIS
30	-1.1694	4.486	
60	-1.1235	4.688	
90	-2.0598	4.862	
120	-4.9738	5.134	
150	-7.3248	5.482	
** 180	-8.0919	5.823	S-TRANS
210	-7.1987	6.096	
240	-4.2426	5.973	
270	-0.3862	5.032	
300	0.0060	4.640	
330	-0.2453	4.502	
360	-0.6466	4.451	

** GLOBAL MINIMUM



a. Assume C_1 - C_2 - 0 to form a triangular plane on the x,y axis, z=0 (figure 4)

b. Set up three dummy atoms according to the bond length of C^1C_2, C^10, C^20

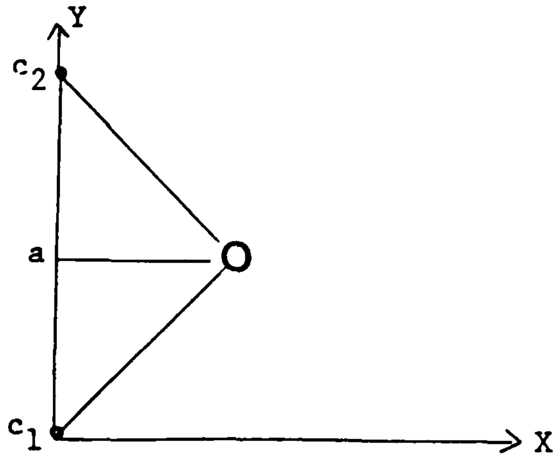


FIGURE 4

c. Form two right triangles and calculate the length 0-a using the phythagorean theorem. Bond lengths C_20, C_10, and C_1C_2 can be obtained from the MM2 output and $aC_1 = 1/2\ C_1C_2$.

By the phythagorean theorem:

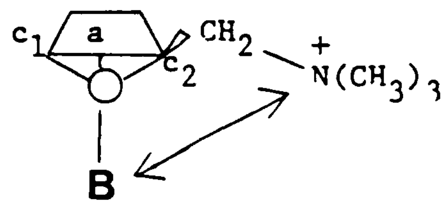
$$(0C_2)_2 = (0a)_2 + (aC_2)_2$$

$$(0a)_2 = (0C_2)_2 - (aC_2)_2$$

$$0a = [(0C_2)_2 - (0C_2)_2]_{1/2}$$

Adding 1.74A + 0a = new distance (a-0-B) in a straight line extension. We then calculate the non-bonding distance from N to

B.



6. Preferred Conformations of Muscarine and its Isomers

Tables II-V show the results of dihedral driver calculations for muscarine, epiallomuscarine, epimuscarine and allomuscarine. The lowest energy (global minimum) structures were given in Chart II. The calculated energies were similar (Table I, about 28 kcal). The ring conformations and the side chain dihedral angles were also similar about 70^{o}). Extended N...O distances (about 3.0A^{o}) were not within the Beers and Reich distance of 4.44A^{o}. Incremental rotation of the side chain and MM2 optimization produced conformers with better N...O distances but higher energies. Those with steric energies within 5 kcal of the lowest are considered most accessible conformers. For muscarine, epiallo-and epimuscarine these are conformations with dihedral angles of 150^{o} and 180^{o}, and for allomuscarine conformations with dihedral angles of 120, 150 and 180^{o}. All of these have extended N...O distances between 4.1 to 4.8A^{o}.

7. Optimization of cis/trans-2,3-dehydromuscarine, cis/trans-Muscarone, and cis/trans-F2268

Tables VI-XI show the results of dihedral driver optimizations for the titled compounds. As for the muscarine isomers, the global minimum structures have extended N...O

distances which are similar and too short (3.1 to 3.5A^{o}), and

similar dihedral angles (about $\pm 70^{\circ}$). Potential bioactive conformations for all of the above except trans-F2268 have dihedral angles of 120, 150 and 180° and extended distances between 4.1 to 5.0A°. Trans-F2268 has the best extended N...0 distances (4.3 to 4.94A°) at dihedral angles of 180° and 210°. Trans-muscarone can achieve the potential bioactive conformations with difficulty since the difference in steric energy between the lowest energy conformer and these varies by 6 to 16 kcal. The extended N...0 distances for the trans isomer are also a bit high. (4.9 to 5.0A°).

8. Optimization of 5-methylfurmethide, TFTM, F-2581 and Arecoline Derivatives

The 5-membered ring agonists, 5-methylfumethide and TFTM (Tables XII and XIII) are analogous to the muscarine analogs with global minimum structures having dihedral angles of about 70° and extended N...0 distances between 3.0 - 4.0A°. Better N...0 distances are obtained for conformers with dihedral angles between 120 and 240° (N...0 4.3 to 4.6A°). For TFTM however, to attain the projected bioconformations a distortion of 6 to 9 kcal of energy must occur.

F2581 (Table XIV) has fewer conformational possibilities. The six membered ring exists as a chair, and for the 1,4 trans isomer the two substituents are preferentially in diequatorial positions. However, the diequatorial isomer (energy 33.08 kcal) doesnotfit the bioactive scheme (extended N...0 distance of 5.1A°). When we attempted to model the diaxial conformer we did not get a final energy and the extended N...O distance was too

short, 3.67A^{o}.

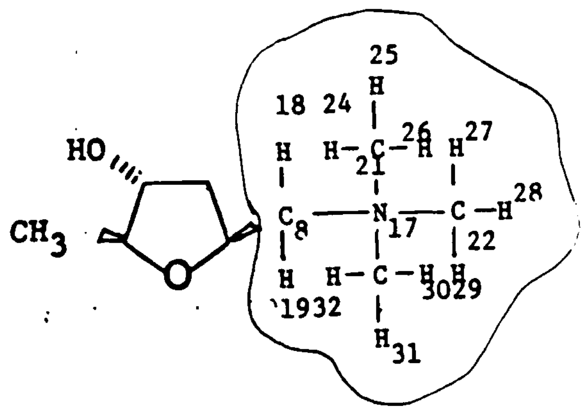
The arecoline derivatives (Tables XV-XVII) that we modeled included the NH_2, monomethyl and dimethyl ammonium salts. The best ring conformation for all of these analogs was a half-chair. The global mimimum for all of the congeners (NH_2, NH, CH_3 and N-CH_3, CH_3) was the s-trans conformer (180^{o} dihedral angle indicated by asteriscs). Although this conformation had the lowest energy, in each case the extended N...O distances were too high (5.6 - 5.8A^{o}).

It has been proposed that the muscarinic receptor binds to the quaternary ammonium group and to the ester ether oxygen while the nicotinic receptor binds to the ester carbonyl oxygen.(11) The conformers with dihedral angles between 0-60^{o} had the best extended N...O distances, 4.4 to 4.7A^{o}, but their energies were high (7 to 8 kcal higher). We don't know at this point whether binding to the receptor can lower these energy differences. Perhaps binding could occur initially by hydrogen bonding to the oxygen of the s-trans conformation, followed by rotation around the single bond to achieve the coulombic interaction at the quaternary nitrogen.

9. Calculation of Partial Charges

Partial charges were calculated for the molecules in Chart I. For all cases MOPAC (MINDO) was used, and in some cases MINDO and CNDO charges were derived as well. We were testing various methodsfor partialcharge generation. Tables XVIII - XXIII give the results of partial charges calculated by the different methods. Charges were calculated for the lowest energy conformation and for all the most probable bioconformations (those with extended N...O

distances around 4.0 - 4.8A° and within 7 kcal from the global minimum). These results are given in Appendix A. Cationic head charges were calculated for the various conformers. An example of this calculation is illustrated for muscarine. The cationic head is illustrated below and is within the enclosed region.



Taking the sum of the charges in that region gives a charge of 0.917 for muscarine. A comparion of MNDO and CNDO data indicates a better correlation with literature data for MNDO derived charges. It is well known that for tetrasubstitued nitrogens, the positive charge resides on the peripheral methyls and hydrogens and not on the nitrogen.[12] MNDO calculations agree with this result, while CNDO calculations give a positive nitrogen. MINDO calculations are very similar to MNDO. As can be seen from Tables XVIII to XXIII, and Appendix A there is a small variation in cationic head charge with isomer, conformation and agonist. A larger head charge would result in a better agonist-receptor interaction. Muscarine and its Cis/trans isomers epiallomuscarine, epimuscarine and allomuscarine all have similar cationic head charges of about 0.9 esu., while their dehydro analogs, cis/trans 2,3 dehydromuscarine have slightly larger cationic charges, 1.0 esu. The cationic head charges for cis/trans muscarone are about 0.94 esu for all conformers.

TABLE XVIII

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

MUSCARINE(GLOBAL MINIMUM)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE (MNDO)
1	O	-0.2528	-0.3299	-0.3314	0.917
2	C	0.1521	0.0747	0.0777	
3	C	0.1520	0.1126	0.0929	
4	C	-0.0170	-0.0347	-0.0321	
5	C	0.1561	0.1061	0.0921	
6	C	-0.0328	0.0269	0.0207	
7	O	-0.2647	-0.3162	-0.3191	
8	C	0.0599	0.0928	0.0679	
9	N	0.0952	-0.1505	-0.0836	
10	C	0.0530	0.1064	0.0813	
11	C	0.0541	0.1051	0.0828	
12	C	0.0544	0.1241	0.0862	
13	H	-0.0039	0.0403	0.0461	
14	H	-0.0083	0.0378	0.0491	
15	H	0.0177	0.0290	0.0353	
16	H	0.0283	0.0551	0.0603	
17	H	-0.0096	0.0346	0.0393	
18	H	0.0260	0.0151	0.0178	
19	H	0.0176	0.0184	0.0209	
20	H	0.0141	0.0072	0.0053	
21	H	0.1580	0.2067	0.1957	
22	H	0.0324	0.0518	0.0608	
23	H	0.0406	0.0667	0.0717	
24	H	0.0548	0.0544	0.0593	
25	H	0.0520	0.0552	0.0594	
26	H	0.0514	0.0619	0.0665	
27	H	0.0527	0.0565	0.0615	
28	H	0.0509	0.0545	0.0592	
29	H	0.0518	0.0586	0.0623	
30	H	0.0612	0.0618	0.0671	
31	H	0.0476	0.0686	0.0771	
32	H	0.0552	0.0481	0.0508	

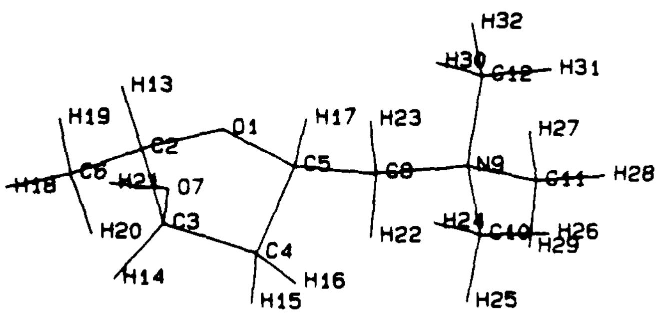


TABLE XIX

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

+EPIALLOMUSCARINE(LOCAL MINIMUM 162 DEG.)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE (MNDO)
1	O	-0.2273	-0.3131	-0.2963	
2	C	0.1605	0.0910	0.0796	0.903
3	C	0.1525	0.1112	0.0950	
4	C	-0.0259	-0.0433	-0.0451	
5	C	0.1520	0.1201	0.0996	
6	C	-0.0321	0.0372	0.0261	
7	O	-0.2623	-0.3080	-0.3150	
8	C	0.0583	0.0726	0.0487	
9	N	0.0964	-0.1509	-0.0837	
10	C	0.0518	0.1092	0.0805	
11	C	0.0546	0.1088	0.0832	
12	C	0.0528	0.1123	0.0809	
13	H	-0.0203	0.0168	0.0227	
14	H	-0.0072	0.0314	0.0486	
15	H	0.0086	0.0215	0.0260	
16	H	0.0137	0.0502	0.0481	
17	H	-0.0071	0.0298	0.0429	
18	H	0.0226	0.0087	0.0101	
19	H	0.0232	0.0232	0.0197	
20	H	0.0220	0.0180	0.0257	
21	H	0.1588	0.2033	0.1971	
22	H	0.0349	0.0537	0.0645	
23	H	0.0383	0.0746	0.0777	
24	H	0.0537	0.0560	0.0618	
25	H	0.0518	0.0561	0.0600	
26	H	0.0530	0.0586	0.0621	
27	H	0.0514	0.0566	0.0611	
28	H	0.0538	0.0566	0.0619	
29	H	0.0549	0.0602	0.0649	
30	H	0.0561	0.0634	0.0666	
31	H	0.0547	0.0611	0.0660	
32	H	0.0518	0.0533	0.0587	

+same numbering scheme as muscarine

TABLE XX

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

+EPIMUSCARINE(LOCAL MINIMUM 151 DEG.)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE (MNDO)
1	O	-0.2273	-0.3060	-0.2936	
2	C	0.1602	0.0872	0.0796	0.915
3	C	0.1504	0.1075	0.0867	
4	C	-0.0260	-0.0482	-0.0460	
5	C	0.1537	0.1174	0.1068	
6	C	-0.0324	0.0387	0.0281	
7	O	-0.2700	-0.3170	-0.3258	
8	C	0.0603	0.0848	0.0460	
9	N	0.0957	-0.1517	-0.0858	
10	C	0.0531	0.1082	0.0821	
11	C	0.0544	0.1104	0.0840	
12	C	0.0530	0.1062	0.0820	
13	H	-0.0140	0.0225	0.0308	
14	H	-0.0054	0.0362	0.0519	
15	H	0.0044	0.0358	0.0350	
16	H	0.0216	0.0341	0.0453	
17	H	-0.0174	0.0178	0.0253	
18	H	0.0231	0.0097	0.0119	
19	H	0.0230	0.0207	0.0274	
20	H	0.0198	0.0187	0.0147	
21	H	0.1591	0.2062	0.1981	
22	H	0.0418	0.0680	0.0828	
23	H	0.0400	0.0752	0.0783	
24	H	0.0544	0.0585	0.0640	
25	H	0.0514	0.0549	0.0587	
26	H	0.0514	0.0553	0.0583	
27	H	0.0511	0.0557	0.0591	
28	H	0.0540	0.0584	0.0636	
29	H	0.0547	0.0599	0.0644	
30	H	0.0559	0.0618	0.0664	
31	H	0.0547	0.0599	0.0624	
32	H	0.0513	0.0581	0.0573	

+ same numbering scheme as muscarine

TABLE XXI

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

+ALLOMUSCARINE(LOCAL MINIMUM 131 DEG.)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE (MNDO)
1	O	-0.2313	-0.3127	-0.2904	
2	C	0.1504	0.0810	0.0671	0.903
3	C	0.1486	0.1012	0.0869	
4	C	-0.0234	-0.0385	-0.0379	
5	C	0.1539	0.1130	0.0954	
6	C	-0.0312	0.0300	0.0262	
7	O	-0.2748	-0.3223	-0.3338	
8	C	0.0561	0.0733	0.0324	
9	N	0.0963	-0.1536	-0.0843	
10	C	0.0525	0.1076	0.0821	
11	C	0.0541	0.1111	0.0838	
12	C	0.0526	0.1125	0.0823	
13	H	-0.0124	0.0345	0.0328	
14	H	-0.0063	0.0399	0.0511	
15	H	0.0136	0.0442	0.0425	
16	H	0.0288	0.0431	0.0537	
17	H	-0.0159	0.0328	0.0445	
18	H	0.0233	0.0113	0.0128	
19	H	0.0200	0.0133	0.0138	
20	H	0.0224	0.0231	0.0268	
21	H	0.1597	0.2053	0.1995	
22	H	0.0396	0.0633	0.0813	
23	H	0.0422	0.0692	0.0744	
24	H	0.0534	0.0577	0.0629	
25	H	0.0527	0.0556	0.0600	
26	H	0.0524	0.0559	0.0596	
27	H	0.0513	0.0557	0.0597	
28	H	0.0538	0.0564	0.0633	
29	H	0.0544	0.0598	0.0635	
30	H	0.0557	0.0601	0.0664	
31	H	0.0563	0.0635	0.0650	
32	H	0.0511	0.0531	0.0569	

+same numbering scheme as muscarine

TABLE XXII

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

DEHYDRO-MUSCARINE(GLOBAL MINIMUM) (TRANS)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE (MNDO)
1	O	-0.2299	-0.2665	-0.2439	
2	C	0.1638	0.0802	0.0981	
3	C	0.1551	0.1414	0.1329	1.005
4	C	-0.0601	-0.0965	-0.1301	
5	C	0.1339	-0.0354	-0.0361	
6	C	-0.0374	0.0195	0.0011	
7	O	-0.2612	-0.3089	-0.3049	
8	C	0.0673	0.1744	0.1433	
9	N	0.0985	-0.1548	-0.0870	
10	C	0.0520	0.1099	0.0804	
11	C	0.0529	0.1066	0.0811	
12	C	0.0524	0.1177	0.0810	
13	H	0.0059	0.0596	0.0817	
14	H	-0.0053	0.0427	0.0547	
15	H	0.0184	0.1051	0.0912	
16	H	0.0290	0.0180	0.0243	
17	H	0.0215	0.0232	0.0254	
18	H	0.0112	0.0085	0.0006	
19	H	0.1582	0.2041	0.1931	
20	H	0.0392	0.0564	0.0670	
21	H	0.0431	0.0721	0.0760	
22	H	0.0527	0.0542	0.0598	
23	H	0.0587	0.0674	0.0758	
24	H	0.0524	0.0526	0.0557	
25	H	0.0521	0.0570	0.0628	
26	H	0.0526	0.0550	0.0590	
27	H	0.0538	0.0578	0.0621	
28	H	0.0639	0.0707	0.0846	
29	H	0.0502	0.0482	0.0542	
30	H	0.0551	0.0601	0.0622	

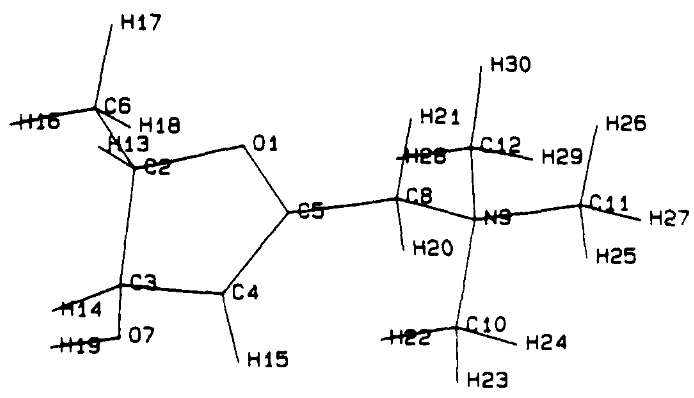


TABLE XXIII

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

+DEHYDRO-MUSCARINE (CIS)-(GLOBAL MINIMUM)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE(MNDO)
1	O	-0.2272	-0.2639	-0.2407	1.008
2	C	0.1665	0.0797	0.0696	
3	C	0.1526	0.1391	0.1311	
4	C	-0.0541	-0.0847	-0.0991	
5	C	0.1311	-0.0399	-0.0425	
6	C	-0.0346	0.0371	0.0290	
7	O	-0.2606	-0.3092	-0.3076	
8	C	0.0673	0.1757	0.1428	
9	N	0.0986	-0.1543	-0.0871	
10	C	0.0514	0.1093	0.0791	
11	C	0.0530	0.1066	0.0819	
12	C	0.0529	0.1168	0.0818	
13	H	-0.0119	0.0361	0.0375	
14	H	-0.0033	0.0404	0.0556	
15	H	0.0181	0.1065	0.0937	
16	H	0.0261	0.0153	0.0153	
17	H	0.0210	0.0157	0.0192	
18	H	0.0204	0.0178	0.0234	
19	H	0.1590	0.2040	0.1963	
20	H	0.0397	0.0572	0.0682	
21	H	0.0427	0.0717	0.0766	
22	H	0.0525	0.0543	0.0597	
23	H	0.0588	0.0662	0.0761	
24	H	0.0530	0.0536	0.0567	
25	H	0.0520	0.0565	0.0626	
26	H	0.0529	0.0550	0.0593	
27	H	0.0540	0.0587	0.0621	
28	H	0.0502	0.0479	0.0543	
29	H	0.0555	0.0609	0.0630	
30	H	0.0623	0.0697	0.0820	

+same numbering scheme as trans dehydro-muscarine

The cationic head charge of 5-methylfurmethide (1.02 esu) coincides with that of 2,3 dehydromuscarine, while the cationic head charge of TFTM is closer to muscarine and its isomers (0.93 esu). Arecoline, H,H, H,CH_3, and CH_3,CH_3 is also close to muscarine (0.92 esu).

10. Derivation of Electrostatic Potential Contours

Electrostatic Potential[18] contours were generated from the MNDO charges for the lowest energy and the possible bioactive conformations of the agonists in Chart I. Table XXIV summarizes the agonists, steric energies, dihedral angles, N...0 distances, and electrostatic contour levels that were generated. Most of the electrostatic potentials were contoured at 20,30,100, and 150 kcals and some at 30,120 and 160 as well. Electrostatic potentials were generated as repulsive potentials to an incoming positive charge: the larger the potential the more positive the area, and increased binding to the receptor might be expected. Since there is a net charge of +1 on these agonists, there are no negative potentials but there are areas of more or less positive charge. We checked the conformations for the highest and lowest contouring values. The largest potential obtained for any of the agonists is 160 kcal. The lowest potential falls at 20 kcal. The most positive region is always around the methyl and methylene substituents on the nitrogen (cationic head). The lowest potentials are found near the oxygens. This substantiates the idea of coulomic interaction occuring at the amino group and hydrogen bonding interaction at the oxygens. From the plotted maps it is difficult to see significant differences. We plan to

Table XXIV

Muscarinic Agonists

	Compound	[a]Steric Energy	[b]Dihedral Angle	[c]N...O Dist.	[d]Electrostatic Contour
1.	Muscarine	27.71	73.25	3.06	20,40,100,150
		30.06	150	4.3	20,40,100,150
		30.39	180	4.41	30,40,100,150
2.	2 Epimuscarine	31.09	180	4.43	20,40,100,150
		29.52	151	4.32	20,40,100,150
3.	Allomuscarine	31.12	120	4.14	20,40,100,150
		31.30	131.63	4.45	20,40,100,150
		30.79	150	4.53	20,40,100,150
		32.80	180	4.8	20,40,100,150
		28.42	65	3.01	20,40,100,150
4.	Epiallomuscarine	27.90	70	3.05	20,40,100,150
		30.26	150	4.28	20,40,100,150
		30.30	162	4.43	20,40,100,150
		30.58	180	4.48	30,40,100,150
5.	Dehydromuscarine (trans)	16.94	120	4.20	30,40,100,150
		18.64	150	4.53	30,40,100,150
		18.56	180	4.68	30,40,100,150
6.	Dehydromuscarine (cis)	17.25	120	4.21	20,40,100,150
		18.99	180	4.68	30,40,100,150
		19.56	240	4.40	30,40,100,150
		14.94	270	4.01	30,40,100,150
7.	Muscarone (trans)	31.84	287.18	3.1	30,50,70,100 120,160

Table XXIV

	Compound	[a]Steric Energy	[b]Dihedral Angle	[c]N...O Dist.	[d]Electrostatic Contour
8.	Muscarone	31.14	72.25	3.13	30,50,70,100,120,160
	(cis)	33.47	150.00	4.3	30,50,70,100,120,160
		33.30	180	4.43	30,50,70,100,120,160
9.	F-2268 (cis)		150		30,50,70,100,120,160
		25.03	180	4.47	30,50,70,100,120,160
10.	F-2268 (trans)	22.68	286.62	3.13	30,50,70,100,120,160
		25.30	180	4.48	30,50,70,100,120,160
		26.81	210	4.27	30,50,70,100,120,160
11.	5-Methyl-furmethide	4.94	72.3	3.59	20,30,100,150
		7.8	120	4.29	20,30,100,150
		9.66	150	4.55	20,30,100,150
12.	TFTM	25.74	71.38	3.05	20,30,100,150
		28.32	150.00	4.27	20,30,100,150
		28.50	180.00	4.46	20,30,100,150

a. reported in kilocalories/mole
b. reported in degrees
c. reported in Angstroms (A°)
d. reported in kilocalories

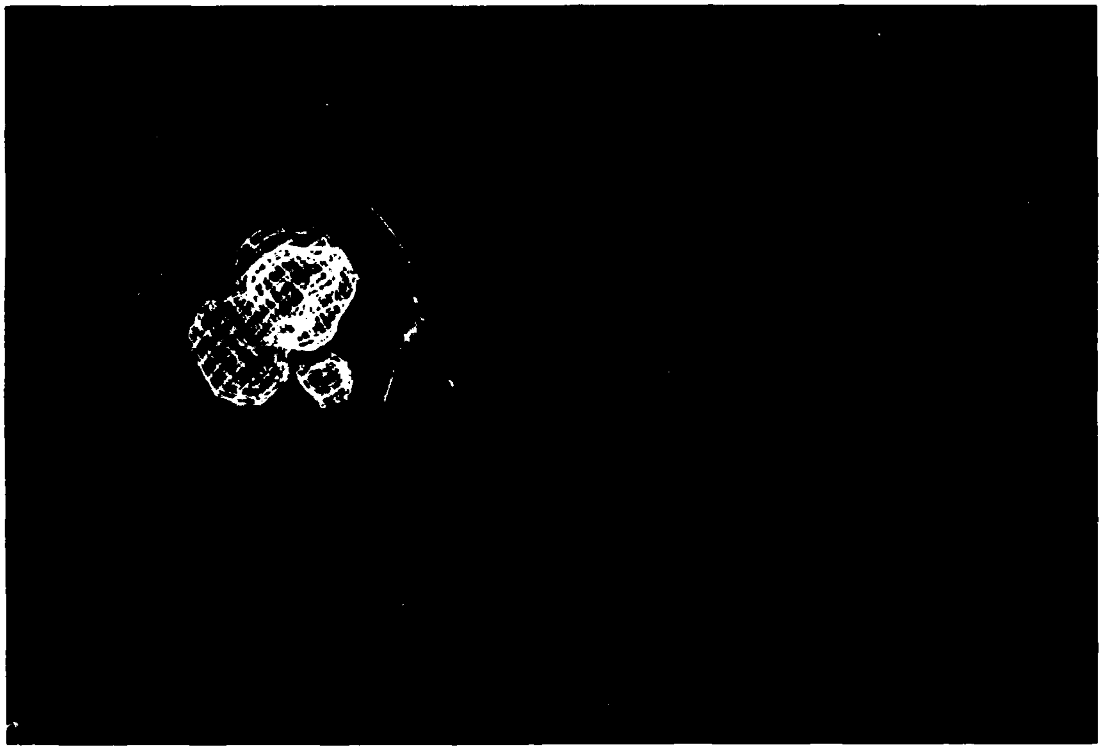


Figure 5. Muscarine (150 dihedral angle) - Electrostatic Potential Contour. Contoured at 150 kcal, 100 kcal, 40 kcal, and 20 kcal. Most positive region is found within the 150 kcal enclosure ($N-CH_3$ groups). Least positive areas are found in the 20 kcal region (oxygens, ring and OH).

Color Coding: yellow, 150 kcal; red, 100 kcal; blue, 40 kcal; light bulue, 20 kcal

compute electrostatic potential difference maps to unveil subtle differences in the electrostatic field for different analogs.

The methodology is illustrated in figure 5 where illustrations for muscarine are given. Muscarine has a maximum electrostatic potential of 150 kcals: this region is shown in black and surrounds the N-methyls. The lowest potentials are found around the ring oxygens and these are shown in red.

Conclusions

The five membered ring cyclic analogs of muscarine show the same general conformational trends. The lowest energy (global minimum) for each 5 membered cyclic agonist falls at a dihedral angle of about 70° ($\pm 5^{\circ}$). These minimum energy structures, however, all possess extended N...O distances substantially smaller than the 4.44A$^{\circ}$ required for muscarine activity according to the Beers and Reich hypothesis[11]. To achieve the requisite N...O distance, rotation of the side chain is needed. The conformations with an appropriate extended N...O distance (4.4A$^{\circ}$ $\pm$.4) usually fall at dihedral angles of 120-210°, with preference for most cases at 150-180°. However, with this rotation an increase in steric energy is observed. The energies vary from 2 to 16 kcal above the minimum. We tentatively conclude the most probable bioactive conformations possess dihedral angles between 150-180°.

For some of the agonists these conformations are difficult to achieve due to a large energy barrier: this is true for *trans*-dehydromuscarine, and for *trans* muscarone.

At this point it is not clear how the conformational aspects

govern activity. All of these molecules have other functional groups which could be involved in binding, perhaps to another site. Schulman, Sabio, and Disch[10] have performed calculations on some of the same molecules and have reached similar conclusions.

Partial charge calculations and electrostatic potential energies agree that where another carbonyl, hydroxyl or ether oxygen is present, this is a high electron density region and thus possibly subject to an additional hydrogen bonding interaction, which potentiates the binding to the muscarinic receptor. Alternatively it could hinder binding if that binding is to other than the muscarinic receptor. The molecule might compete for which receptor to bind to.

V. FUTURE GOALS

In the following year the work will progress in the ways described below.

With our conformational work nearly finished on several of the representative agonists, we will proceed to perform receptor mapping studies. This work will be started using SYBYL procedures on the molecules we modeled thus far. We are starting the modeling of muscarinic antagonists and the comparison of agonist/antagonist conformational and electronic properties.

We will begin designing new antagonists and look for sterically constrained agonists/antagonists. An unexplained problem is what effect on binding is there by remote functional groups such as the OH in muscarine and its isomers, the carbonyl in muscarone, the ether oxygen in F2268 and the double bond in 2-3-dehydromuscarine. We will try to investigate the problem by careful calculation of electronic properties of these molecules and by fitting them into derived receptor surfaces.

Conformational work will proceed by superposition of agonists/antagonists. Electrostatic effects will be studied by deriving electrostatic potential difference maps. A close investigation and correlation with muscarinic activity vs. agonist/antagonist and conformation and electronic properties will be made.

A thorough literature search will be made for obtaining new ligands to fit into our scheme.

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APPENDIX A

MNDO CHARGE CALCULATIONS

MNDO CHARGES - MUSCARINE (GLOBAL MINIMUM)

		x	y	z	charge
1	O	2.7422	-0.0747	3.5455	-0.3323
2	C	3.3868	-0.6266	2.4075	0.0776
3	C	3.6946	0.6787	4.2713	0.0911
4	C	4.7018	0.1445	2.2117	0.0931
5	C	2.4326	-0.5062	1.2161	0.0218
6	H	3.5771	-1.7024	2.6381	0.0449
7	C	4.5523	1.3220	3.1766	-0.0318
8	C	3.0029	1.7083	5.1821	0.0690
9	H	4.3124	-0.0425	4.8560	0.0393
10	O	5.7831	-0.6459	2.6585	-0.3187
11	H	4.9139	0.4595	1.1620	0.0485
12	H	2.8842	-0.9503	0.2994	0.0179
13	H	1.4733	-1.0373	1.4156	0.0205
14	H	2.1953	0.5615	1.0029	0.0063
15	H	3.9937	2.1510	2.6805	0.0348
16	H	5.5262	1.7135	3.5542	0.0608
17	N	2.2504	1.1917	6.3811	-0.0833
18	H	3.7898	2.4165	5.5339	0.0609
19	H	2.3084	2.3042	4.5440	0.0708
20	H	6.0820	-1.1921	1.9475	0.1955
21	C	3.1692	0.4891	7.3330	0.0813
22	C	1.6331	2.3620	7.0899	0.0826
23	C	1.1592	0.2522	5.9698	0.0861
24	H	3.6022	-0.4332	6.8858	0.0666
25	H	4.0083	1.1541	7.6419	0.0592
26	H	2.6242	0.1761	8.2533	0.0593
27	H	0.9236	2.9056	6.4242	0.0622
28	H	1.0656	2.0345	7.9914	0.0615
29	H	2.4127	3.0843	7.4256	0.0592
30	H	1.5694	-0.6846	5.5313	0.0785
31	H	0.5443	-0.0508	6.8484	0.0505
32	H	0.4807	0.7288	5.2253	0.0662

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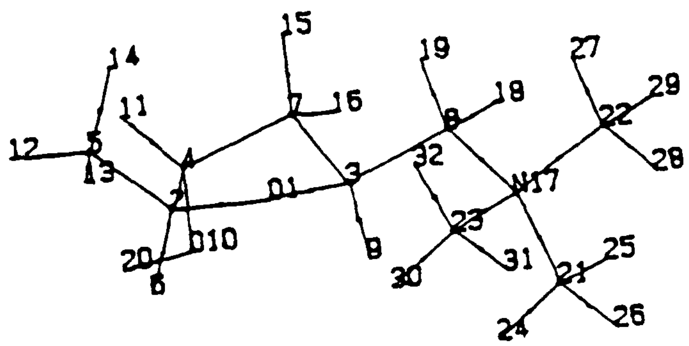

MNDO CHARGES - MUSCARINE (150°dihed. angle)

		x	y	z	charge
1	O	1.6252	-0.0408	-1.1411	-0.3032
2	C	1.9266	-0.5316	-2.4385	0.0750
3	C	0.2172	-0.0406	-0.9814	0.0973
4	C	0.6680	-1.2437	-2.9580	0.0927
5	C	3.1428	-1.4558	-2.3318	0.0225
6	H	2.1771	0.3577	-3.0657	0.0461
7	C	-0.2273	-1.3083	-1.7178	-0.0421
8	C	-0.1237	0.0271	0.5208	0.0595
9	H	-0.1354	0.8679	-1.5216	0.0305
10	O	0.0267	-0.4342	-3.9215	-0.3216
11	H	0.8498	-2.2436	-3.4197	0.0469
12	H	3.4321	-1.8483	-3.3337	0.0149
13	H	4.0216	-0.9152	-1.9105	0.0266
14	H	2.9248	-2.3249	-1.6693	0.0058
15	H	0.0254	-2.2155	-1.1198	0.0366
16	H	-1.3115	-1.3352	-1.9724	0.0448
17	N	-1.4082	0.7046	0.9243	-0.0854
18	H	-0.1067	-1.0128	0.9222	0.0665
19	H	0.7144	0.5568	1.0324	0.0790
20	H	0.4594	-0.5498	-4.7542	0.1963
21	C	-2.5850	0.0593	0.2637	0.0795
22	C	-1.5614	0.5771	2.4125	0.0835
23	C	-1.3841	2.1634	0.5791	0.0812
24	H	-2.5575	0.2075	-0.8388	0.0652
25	H	-2.6098	-1.0347	0.4746	0.0613
26	H	-3.5403	0.5030	0.6274	0.0607
27	H	-0.7074	1.0541	2.9468	0.0647
28	H	-2.4979	1.0677	2.7653	0.0616
29	H	-1.6065	-0.4929	2.7212	0.0617
30	H	-1.3397	2.3325	-0.5194	0.0672
31	H	-2.3050	2.6731	0.9454	0.0588
32	H	-0.5066	2.6696	1.0433	0.0659

$ T MUS180N.OUT

MNDO CHARGE - MUSCARINE (180^{o} dihe. angle)

		x	y	z	charge
1	O	1.6284	-0.0788	-1.0983	-0.3046
2	C	1.9776	-0.4788	-2.4127	0.0761
3	C	0.2147	-0.0371	-0.9938	0.0986
4	C	0.7363	-1.1464	-3.0198	0.0944
5	C	3.1869	-1.4137	-2.3242	0.0233
6	H	2.2516	0.4514	-2.9663	0.0473
7	C	-0.2307	-1.2336	-1.8363	-0.0468
8	C	-0.1361	-0.0295	0.5075	0.0580
9	H	-0.0991	0.9205	-1.4753	0.0387
10	O	0.1616	-0.2898	-3.9842	-0.3201
11	H	0.9219	-2.1332	-3.5074	0.0457
12	H	3.5110	-1.7396	-3.3392	0.0149
13	H	4.0512	-0.9066	-1.8365	0.0274
14	H	2.9431	-2.3240	-1.7296	0.0046
15	H	-0.0658	-2.1833	-1.2745	0.0306
16	H	-1.2879	-1.1724	-2.1819	0.0442
17	N	-1.5800	0.0141	0.9373	-0.0841
18	H	0.3536	-0.9129	0.9810	0.0727
19	H	0.3804	0.8662	0.9280	0.0739
20	H	0.6494	-0.3647	-4.7906	0.1965
21	C	-2.2921	-1.2748	0.6663	0.0804
22	C	-1.6163	0.2494	2.4212	0.0829
23	C	-2.2992	1.1352	0.2547	0.0797
24	H	-2.4112	-1.4670	-0.4194	0.0629
25	H	-1.7501	-2.1362	1.1200	0.0634
26	H	-3.3223	-1.2571	1.0911	0.0596
27	H	-1.1287	1.2148	2.6903	0.0643
28	H	-2.6642	0.2924	2.7986	0.0613
29	H	-1.0902	-0.5666	2.9688	0.0637
30	H	-2.3530	0.9694	-0.8451	0.0652
31	H	-3.3463	1.2221	0.6260	0.0600
32	H	-1.7865	2.1076	0.4379	0.0654

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MNDO CHARGES - EPIALLOMUSCARINE (70^{o}) (GLOBAL MIN.)

		x	y	z	charge
1	O	1.6212	-0.0344	-1.1745	-0.3305
2	C	1.9218	-0.8155	-2.3205	0.0818
3	C	0.2180	-0.0221	-0.9776	0.0925
4	C	0.5890	-1.2577	-2.9372	0.0938
5	C	2.8491	-0.0288	-3.2487	0.0229
6	H	2.4568	-1.7136	-1.9269	0.0324
7	C	-0.3101	-1.2668	-1.7011	-0.0327
8	C	-0.1302	0.0103	0.5209	0.0653
9	H	-0.1621	0.8857	-1.5009	0.0408
10	O	0.1014	-0.2783	-3.8285	-0.3176
11	H	0.6271	-2.2362	-3.4740	0.0511
12	H	3.0828	-0.6187	-4.1646	0.0137
13	H	2.3869	0.9347	-3.5630	0.0160
14	H	3.8112	0.2118	-2.7402	0.0193
15	H	-0.1238	-2.1857	-1.0959	0.0344
16	H	-1.3968	-1.2047	-1.9457	0.0603
17	N	0.1618	1.2765	1.2842	-0.0824
18	H	-1.2192	-0.2147	0.6102	0.0600
19	H	0.4055	-0.8410	1.0034	0.0691
20	H	0.4251	-0.4612	-4.6975	0.1965
21	C	-0.6358	2.4260	0.7483	0.0813
22	C	-0.2201	1.0596	2.7195	0.0827
23	C	1.6179	1.6208	1.2235	0.0859
24	H	-0.3411	2.6859	-0.2926	0.0678
25	H	-1.7255	2.1930	0.7548	0.0587
26	H	-0.4780	3.3407	1.3651	0.0590
27	H	0.3646	0.2236	3.1683	0.0619
28	H	-0.0278	1.9714	3.3308	0.0614
29	H	-1.3028	0.8122	2.8135	0.0590
30	H	1.9315	1.8938	0.1914	0.0800
31	H	1.8447	2.5011	1.8680	0.0503
32	H	2.2449	0.7690	1.5745	0.0654

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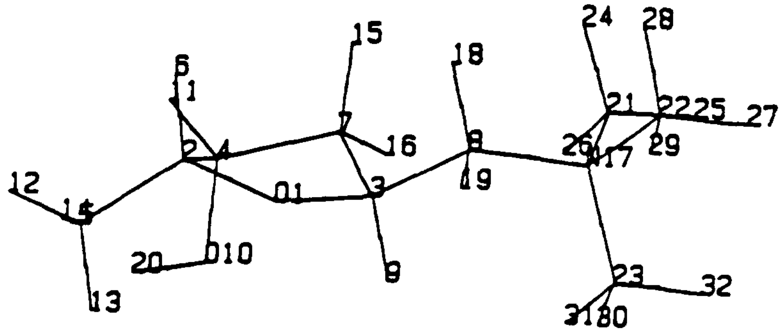

MNDO CHARGES - EPIALLOMUSCARINE (150°)

		x	y	z	charge
1	O	1.6226	-0.0334	-1.1483	-0.3010
2	C	1.9646	-0.8030	-2.2898	0.0790
3	C	0.2128	-0.0361	-0.9870	0.0987
4	C	0.6543	-1.2525	-2.9473	0.0936
5	C	2.9122	-0.0022	-3.1851	0.0229
6	H	2.4953	-1.6994	-1.8869	0.0337
7	C	-0.2847	-1.2762	-1.7407	-0.0443
8	C	-0.1228	0.0274	0.5160	0.0550
9	H	-0.1219	0.8867	-1.5135	0.0348
10	O	0.1801	-0.2755	-3.8485	-0.3201
11	H	0.7176	-2.2268	-3.4891	0.0493
12	H	3.1776	-0.5838	-4.0976	0.0103
13	H	2.4514	0.9596	-3.5067	0.0160
14	H	3.8572	0.2425	-2.6474	0.0260
15	H	-0.1127	-2.2021	-1.1427	0.0349
16	H	-1.3568	-1.2339	-2.0404	0.0449
17	N	-1.4064	0.7020	0.9262	-0.0846
18	H	-0.1051	-1.0149	0.9110	0.0642
19	H	0.7168	0.5534	1.0290	0.0795
20	H	0.5989	-0.4016	-4.6867	0.1973
21	C	-2.5855	0.0704	0.2572	0.0798
22	C	-1.5613	0.5581	2.4126	0.0836
23	C	-1.3759	2.1644	0.5967	0.0811
24	H	-2.5634	0.2415	-0.8418	0.0646
25	H	-2.6111	-1.0272	0.4480	0.0609
26	H	-3.5390	0.5084	0.6324	0.0603
27	H	-0.7051	1.0243	2.9529	0.0647
28	H	-2.4953	1.0497	2.7706	0.0613
29	H	-1.6123	-0.5152	2.7087	0.0613
30	H	-1.3277	2.3451	-0.4998	0.0679
31	H	-2.2958	2.6735	0.9662	0.0582
32	H	-0.4981	2.6627	1.0687	0.0660

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MNDO CHARGES - EPIALLOMUSCARINE (162° dihed. angle)

		x	y	z	charge
1	O	2.0531	0.4023	2.3694	-0.2963
2	C	3.2107	0.3144	1.5583	0.0796
3	C	2.4190	0.2999	3.7393	0.0996
4	C	4.3090	-0.2884	2.4353	0.0950
5	C	2.8903	-0.4592	0.2784	0.0264
6	H	3.4795	1.3688	1.3043	0.0227
7	C	3.9531	0.3316	3.7864	-0.0454
8	C	1.6719	1.4069	4.5097	0.0487
9	H	2.0540	-0.7106	4.0352	0.0429
10	O	4.1550	-1.6868	2.5396	-0.3150
11	H	5.3499	-0.0705	2.0948	0.0486
12	H	3.7992	-0.5599	-0.3580	0.0104
13	H	2.5101	-1.4813	0.5051	0.0197
14	H	2.1090	0.0648	-0.3191	0.0257
15	H	4.3274	1.3813	3.8346	0.0260
16	H	4.3961	-0.2531	4.6249	0.0481
17	N	1.5378	1.2970	6.0065	-0.0837
18	H	2.1531	2.3791	4.2506	0.0645
19	H	0.6429	1.4579	4.0807	0.0777
20	H	4.5684	-2.1000	1.7969	0.1971
21	C	2.8712	1.2954	6.6838	0.0805
22	C	0.7625	2.4876	6.4941	0.0832
23	C	0.7901	0.0558	6.3876	0.0809
24	H	3.4788	2.1767	6.3743	0.0618
25	H	2.7560	1.3284	7.7917	0.0600
26	H	3.4400	0.3690	6.4551	0.0621
27	H	0.6249	2.4554	7.5996	0.0611
28	H	1.2902	3.4379	6.2476	0.0619
29	H	-0.2508	2.5260	6.0315	0.0649
30	H	-0.2046	0.0181	5.8867	0.0666
31	H	1.3535	-0.8641	6.1139	0.0660
32	H	0.6208	0.0158	7.4883	0.0587

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MNDO CHARGES - EPIALLOMUSCARINE (180°)

		x	y	z	charges
1	O	1.6363	-0.0507	-1.1094	-0.3004
2	C	2.0196	-0.8341	-2.2263	0.0807
3	C	0.2196	-0.0228	-0.9995	0.1003
4	C	0.7412	-1.1674	-2.9988	0.0958
5	C	3.1026	-0.1039	-3.0224	0.0239
6	H	2.4397	-1.7745	-1.7937	0.0281
7	C	-0.2801	-1.1867	-1.8613	-0.0486
8	C	-0.1283	-0.0195	0.5025	0.0521
9	H	-0.0827	0.9459	-1.4650	0.0443
10	O	0.3962	-0.1196	-3.8784	-0.3170
11	H	0.7856	-2.1172	-3.5844	0.0484
12	H	3.4003	-0.6968	-3.9175	0.0098
13	H	2.7496	0.8945	-3.3679	0.0188
14	H	4.0129	0.0592	-2.4006	0.0266
15	H	-0.2088	-2.1497	-1.3024	0.0266
16	H	-1.3145	-1.0437	-2.2511	0.0454
17	N	-1.5710	0.0108	0.9380	-0.0839
18	H	0.3653	-0.9061	0.9658	0.0688
19	H	0.3868	0.8739	0.9298	0.0757
20	H	0.8810	-0.2194	-4.6838	0.1978
21	C	-2.2863	-1.2711	0.6436	0.0810
22	C	-1.6015	0.2166	2.4265	0.0828
23	C	-2.2916	1.1464	0.2810	0.0799
24	H	-2.4195	-1.4356	-0.4452	0.0618
25	H	-1.7398	-2.1430	1.0708	0.0631
26	H	-3.3118	-1.2634	1.0798	0.0594
27	H	-1.1108	1.1754	2.7131	0.0645
28	H	-2.6479	0.2543	2.8085	0.0609
29	H	-1.0754	-0.6113	2.9558	0.0633
30	H	-2.3446	1.0058	-0.8223	0.0645
31	H	-3.3387	1.2239	0.6544	0.0594
32	H	-1.7799	2.1150	0.4855	0.0660

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MNDO CHARGES - EPIMUSCARINE (65°dihed.angle) (Global Min.)

		x	y	z	charge
1	O	1.6329	-0.0365	-1.1291	-0.4026
2	C	2.1155	-1.1079	-1.9167	0.6865
3	C	0.2225	-0.0222	-0.9766	0.1505
4	C	2.1815	-2.2962	-0.9573	0.1928
5	C	2.2255	-2.3675	-1.0563	0.4360
6	H	2.1763	-1.9974	-1.2430	-0.9004
7	C	-0.3179	-1.2854	-1.6739	-0.5285
8	C	-0.1317	0.0139	0.5253	0.0540
9	H	-0.1533	0.8854	-1.5036	0.0360
10	O	3.2648	-2.1434	-0.0650	-0.3112
11	H	2.2576	-3.2940	-1.4528	-0.0174
12	H	2.5537	-3.2361	-1.6720	0.0568
13	H	2.9676	-2.2257	-0.2371	0.0799
14	H	1.2501	-2.6258	-0.5844	0.3726
15	H	-1.1415	-1.7945	-1.1211	0.0097
16	H	-0.6974	-1.0306	-2.6927	0.0432
17	N	0.2591	1.2314	1.3242	-0.0850
18	H	-1.2381	-0.1079	0.5996	0.0688
19	H	0.3145	-0.8896	1.0025	0.0429
20	H	4.0092	-2.6130	-0.4128	0.2095
21	C	-0.3835	2.4670	0.7751	0.0838
22	C	-0.2102	1.0329	2.7365	0.0821
23	C	1.7452	1.4174	1.3433	0.0836
24	H	-0.0132	2.7032	-0.2474	0.0673
25	H	-1.4910	2.3536	0.7284	0.0599
26	H	-0.1560	3.3512	1.4143	0.0575
27	H	-1.3165	0.9045	2.7783	0.0597
28	H	0.2593	0.1307	3.1926	0.0581
29	H	0.0500	1.9082	3.3755	0.0607
30	H	2.1399	1.6932	0.3407	0.0801
31	H	2.0319	2.2472	2.0298	0.0505
32	H	2.2608	0.4925	1.6908	0.0627

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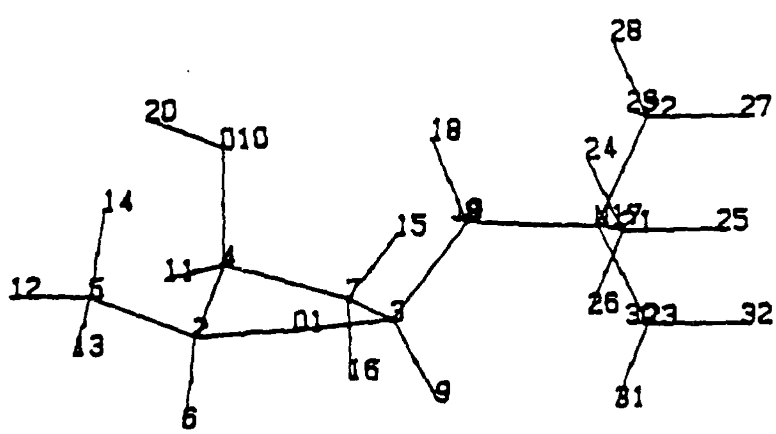

MNDO CHARGES - EPIMUSCARINE (150^{o})

		x	y	z	charge
1	O	1.6530	-0.0834	-1.0085	-0.3690
2	C	2.1565	-1.1892	-1.7333	0.6838
3	C	0.2339	-0.0719	-0.9264	0.1551
4	C	2.1652	-2.3454	-0.7331	0.1998
5	C	2.2117	-2.4190	-0.8255	0.4358
6	H	2.1738	-2.0522	-1.0235	-0.8919
7	C	-0.2708	-1.3490	-1.6212	-0.5706
8	C	-0.1422	0.0392	0.5681	0.0478
9	H	-0.0757	0.8324	-1.4977	0.0268
10	O	3.2156	-2.1871	0.1964	-0.3224
11	H	2.2424	-3.3604	-1.1920	-0.0210
12	H	2.5546	-3.3127	-1.3957	0.0608
13	H	2.9196	-2.2580	0.0200	0.0864
14	H	1.2134	-2.6493	-0.3884	0.3877
15	H	-1.1243	-1.8499	-1.1103	-0.0072
16	H	-0.5824	-1.1207	-2.6687	0.0390
17	N	-1.4308	0.7377	0.9196	-0.0803
18	H	-0.1459	-0.9884	0.9998	0.0437
19	H	0.6859	0.5751	1.0896	0.0675
20	H	3.9975	-2.5793	-0.1654	0.2177
21	C	-2.5982	0.0900	0.2455	0.0835
22	C	-1.6246	0.6493	2.4059	0.0829
23	C	-1.3785	2.1863	0.5379	0.0828
24	H	-2.5195	0.1711	-0.8622	0.0743
25	H	-2.6707	-0.9870	0.5214	0.0615
26	H	-3.5531	0.5807	0.5439	0.0548
27	H	-1.6873	-0.4118	2.7411	0.0583
28	H	-0.7810	1.1328	2.9508	0.0622
29	H	-2.5658	1.1567	2.7202	0.0613
30	H	-1.3066	2.3251	-0.5634	0.0679
31	H	-2.3004	2.7178	0.8689	0.0575
32	H	-0.5056	2.6936	1.0096	0.0634

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MNDO CHARGES - EPIMUSCARINE (180° dihed. angle)

		x	y	z	charge
1	O	1.6596	-0.3016	-0.7886	-0.2931
2	C	2.0717	-0.9451	-1.9785	0.0815
3	C	0.2398	-0.2653	-0.7968	0.0997
4	C	1.1236	-2.1396	-2.0864	0.0977
5	C	3.5618	-1.2816	-1.8959	0.0315
6	H	1.8914	-0.2309	-2.8194	0.0224
7	C	-0.1579	-1.6112	-1.4259	-0.0491
8	C	-0.2223	0.0097	0.6493	0.0594
9	H	-0.0394	0.5835	-1.4667	0.0232
10	O	1.6014	-3.2170	-1.3095	-0.3133
11	H	0.9755	-2.5051	-3.1310	0.0415
12	H	3.8851	-1.8554	-2.7946	0.0107
13	H	4.1754	-0.3528	-1.8430	0.0244
14	H	3.7972	-1.8883	-0.9920	0.0234
15	H	-0.4909	-2.3472	-0.6601	0.0385
16	H	-0.9714	-1.4744	-2.1773	0.0316
17	N	-1.6944	0.1118	0.9627	-0.0854
18	H	0.2175	-0.7925	1.2878	0.0781
19	H	0.2746	0.9583	0.9644	0.0754
20	H	2.2430	-3.6997	-1.8084	0.1946
21	C	-2.4432	-1.1599	0.7165	0.0822
22	C	-1.8322	0.4525	2.4199	0.0829
23	C	-2.3154	1.2086	0.1541	0.0796
24	H	-2.5154	-1.3907	-0.3681	0.0607
25	H	-1.9686	-2.0152	1.2501	0.0690
26	H	-3.4941	-1.0780	1.0779	0.0578
27	H	-1.3920	-0.3460	3.0609	0.0655
28	H	-1.3182	1.4114	2.6619	0.0638
29	H	-2.9023	0.5682	2.7093	0.0607
30	H	-2.2760	0.9780	-0.9346	0.0597
31	H	-3.3874	1.3477	0.4253	0.0604
32	H	-1.7905	2.1771	0.3227	0.0648

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MNDO CHARGES - EPIMUSCARINE (210^{O} dihed.angle)

		x	y	z	charge
1	O	1.6411	-0.0270	-1.0824	-0.2951
2	C	1.9633	-0.4692	-2.3864	0.0813
3	C	0.2249	-0.0243	-0.9741	0.0979
4	C	1.0238	-1.6555	-2.6044	0.0982
5	C	3.4590	-0.7782	-2.4736	0.0315
6	H	1.7071	0.3615	-3.0893	0.0249
7	C	-0.2063	-1.2665	-1.7720	-0.0618
8	C	-0.1221	0.0132	0.5288	0.0613
9	H	-0.1176	0.9105	-1.4800	0.0378
10	O	1.5757	-2.8279	-2.0443	-0.3182
11	H	0.7962	-1.8592	-3.6785	0.0429
12	H	3.7155	-1.1986	-3.4730	0.0107
13	H	4.0639	0.1460	-2.3249	0.0259
14	H	3.7739	-1.5111	-1.6961	0.0218
15	H	-0.4675	-2.1196	-1.1063	0.0334
16	H	-1.0794	-1.0354	-2.4271	0.0364
17	N	-1.3973	-0.6232	1.0231	-0.0846
18	H	0.7351	-0.4519	1.0706	0.0848
19	H	-0.1239	1.0893	0.8254	0.0669
20	H	2.1805	-3.2122	-2.6607	0.1964
21	C	-1.4433	-2.1034	0.8101	0.0710
22	C	-1.4968	-0.3674	2.5007	0.0828
23	C	-2.5780	0.0041	0.3484	0.0794
24	H	-1.5307	-2.3609	-0.2674	0.0744
25	H	-0.5434	-2.5993	1.2413	0.0727
26	H	-2.3404	-2.5472	1.2999	0.0562
27	H	-0.6407	-0.8290	3.0452	0.0659
28	H	-1.4983	0.7247	2.7233	0.0620
29	H	-2.4363	-0.7928	2.9230	0.0607
30	H	-2.5701	-0.1978	-0.7466	0.0587
31	H	-3.5331	-0.4023	0.7541	0.0609
32	H	-2.5844	1.1085	0.4975	0.0627

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MNDO CHARGES - ALLOMUSCARINE (120° dihed angle)

		x	y	z	charge
1	O	1.6243	-0.0164	-1.1581	-0.3008
2	C	2.0913	-1.3379	-1.3801	0.0718
3	C	0.2156	-0.0269	-0.9888	0.1010
4	C	0.8711	-2.2661	-1.3607	0.0842
5	C	2.8407	-1.3616	-2.7169	0.0179
6	H	2.7963	-1.5768	-0.5482	0.0458
7	C	-0.2663	-1.3024	-1.6905	-0.0375
8	C	-0.1084	0.0227	0.5248	0.0417
9	H	-0.1583	0.8663	-1.5365	0.0383
10	O	0.6730	-2.7594	-0.0524	-0.3372
11	H	0.9322	-3.1381	-2.0551	0.0542
12	H	3.2511	-2.3766	-2.9240	0.0142
13	H	2.1690	-1.0831	-3.5609	0.0075
14	H	3.6942	-0.6451	-2.7094	0.0277
15	H	-1.2686	-1.6531	-1.3498	0.0452
16	H	-0.3120	-1.1413	-2.7942	0.0539
17	N	-0.9195	1.1939	1.0125	-0.0863
18	H	-0.6551	-0.9046	0.8098	0.0754
19	H	0.8498	-0.0134	1.0948	0.0803
20	H	1.1559	-3.5694	0.0366	0.2000
21	C	-2.2639	1.2177	0.3533	0.0828
22	C	-1.1170	1.0532	2.4943	0.0846
23	C	-0.1973	2.4805	0.7529	0.0824
24	H	-2.1829	1.3560	-0.7478	0.0597
25	H	-2.8146	0.2667	0.5376	0.0610
26	H	-2.8843	2.0558	0.7464	0.0595
27	H	-1.6583	0.1108	2.7412	0.0622
28	H	-0.1403	1.0386	3.0311	0.0637
29	H	-1.7143	1.9012	2.9021	0.0588
30	H	-0.0650	2.6749	-0.3342	0.0657
31	H	-0.7640	3.3444	1.1704	0.0552
32	H	0.8121	2.4722	1.2251	0.0670

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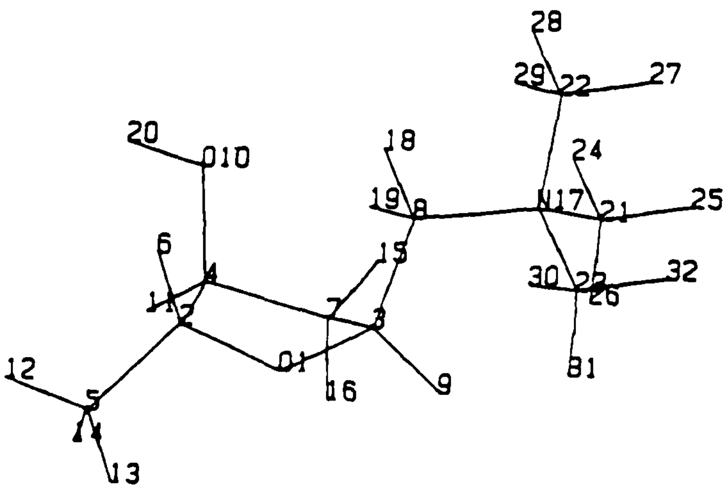

MNDO CHARGES - ALLOMUSCARINE (131^{o} dihed. angle)

		x	y	z	charge
1	O	2.1100	-0.2461	3.2237	-0.2904
2	C	3.1140	0.1998	2.3268	0.0671
3	C	2.6288	-0.2013	4.5396	0.0954
4	C	4.4653	0.0662	3.0453	0.0869
5	C	3.0173	-0.6326	1.0459	0.0262
6	H	2.8828	1.2688	2.1018	0.0328
7	C	4.0993	-0.5984	4.3746	-0.0379
8	C	2.4002	1.2078	5.1351	0.0324
9	H	2.0753	-0.9896	5.0963	0.0445
10	O	4.9886	1.3508	3.3112	-0.3338
11	H	5.2385	-0.5069	2.4792	0.0511
12	H	3.7736	-0.2993	0.2985	0.0128
13	H	3.1934	-1.7120	1.2589	0.0138
14	H	2.0102	-0.5351	0.5787	0.0268
15	H	4.7442	-0.2867	5.2292	0.0425
16	H	4.1769	-1.7068	4.2649	0.0537
17	N	1.8044	1.2781	6.5161	-0.0843
18	H	3.3677	1.7591	5.1362	0.0813
19	H	1.7375	1.7796	4.4438	0.0744
20	H	5.5224	1.6173	2.5760	0.1995
21	C	2.6702	0.5536	7.4989	0.0821
22	C	1.7175	2.7208	6.9229	0.0838
23	C	0.4208	0.7021	6.5326	0.0823
24	H	3.7032	0.9716	7.5018	0.0629
25	H	2.2603	0.6416	8.5313	0.0600
26	H	2.7411	-0.5314	7.2609	0.0596
27	H	1.2806	2.8250	7.9429	0.0597
28	H	2.7254	3.1963	6.9392	0.0633
29	H	1.0760	3.2996	6.2189	0.0635
30	H	-0.2345	1.2169	5.7928	0.0664
31	H	0.4144	-0.3851	6.2989	0.0650
32	H	-0.0438	0.8173	7.5389	0.0569

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MNDO CHARGES - ALLOMUSCARINE (150°)

		x	y	z	charge
1	O	1.6254	-0.0419	-1.1027	-0.2915
2	C	2.1042	-1.3549	-1.3434	0.0700
3	C	0.2144	-0.0533	-0.9624	0.1055
4	C	0.8940	-2.2926	-1.4107	0.0866
5	C	2.9129	-1.3316	-2.6448	0.0185
6	H	2.7724	-1.6149	-0.4878	0.0462
7	C	-0.2589	-1.3269	-1.6734	-0.0416
8	C	-0.1281	0.0495	0.5415	0.0336
9	H	-0.1320	0.8519	-1.5098	0.0377
10	O	0.6899	-2.9031	-0.1538	-0.3362
11	H	0.9729	-3.1041	-2.1734	0.0526
12	H	3.3433	-2.3358	-2.8636	0.0136
13	H	2.2744	-1.0343	-3.5081	0.0075
14	H	3.7576	-0.6075	-2.5787	0.0292
15	H	-1.2356	-1.7248	-1.3172	0.0370
16	H	-0.3395	-1.1385	-2.7708	0.0535
17	N	-1.4191	0.7255	0.9285	-0.0841
18	H	-0.1112	-0.9737	0.9783	0.0848
19	H	0.7052	0.5970	1.0421	0.0748
20	H	1.2303	-3.6794	-0.1082	0.2001
21	C	-2.5932	0.0654	0.2788	0.0821
22	C	-1.5758	0.6236	2.4185	0.0838
23	C	-1.3987	2.1777	0.5574	0.0817
24	H	-2.5521	0.1713	-0.8287	0.0580
25	H	-2.6340	-1.0180	0.5361	0.0658
26	H	-3.5482	0.5305	0.6154	0.0583
27	H	-1.6178	-0.4406	2.7473	0.0641
28	H	-0.7252	1.1135	2.9465	0.0634
29	H	-2.5151	1.1169	2.7597	0.0591
30	H	-1.3539	2.3267	-0.5440	0.0626
31	H	-2.3212	2.6916	0.9135	0.0573
32	H	-0.5236	2.6953	1.0134	0.0660

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MNDO CHARGES - DEHYDROMUSCARINE (TRANS)(GLOBAL MIN.)

		x	y	z	charge
1	O	2.1154	-0.1193	3.1886	-0.2438
2	C	2.8411	-0.3317	1.9864	0.0884
3	C	2.7649	0.8754	3.8632	-0.0361
4	C	4.3056	-0.0289	2.3309	0.1329
5	C	2.2829	0.5940	0.8962	0.0044
6	H	2.6934	-1.3977	1.6891	0.0817
7	C	4.0283	0.9518	3.4234	-0.1304
8	C	2.1620	1.6983	4.9680	0.1433
9	O	4.9291	-1.1723	2.8685	-0.3049
10	H	4.8969	0.3709	1.4735	0.0547
11	H	2.8117	0.4281	-0.0705	0.0243
12	H	1.1993	0.3966	0.7265	0.0254
13	H	2.3939	1.6699	1.1637	0.0006
14	H	4.7926	1.6442	3.8123	0.0912
15	N	1.9224	0.9234	6.2324	-0.0870
16	H	2.8470	2.5522	5.1803	0.0670
17	H	1.2091	2.1375	4.5912	0.0760
18	H	5.8523	-1.1391	2.6719	0.1934
19	C	3.2012	0.3073	6.7085	0.0804
20	C	1.4117	1.8658	7.2797	0.0814
21	C	0.9030	-0.1515	6.0153	0.0810
22	H	3.0483	-0.2287	7.6735	0.0598
23	H	3.5956	-0.4343	5.9770	0.0758
24	H	3.9832	1.0850	6.8686	0.0557
25	H	1.2188	1.3336	8.2397	0.0628
26	H	2.1490	2.6758	7.4860	0.0590
27	H	0.4578	2.3429	6.9563	0.0621
28	H	1.2636	-0.9263	5.3030	0.0846
29	H	0.6724	-0.6771	6.9705	0.0542
30	H	-0.0486	0.2733	5.6207	0.0622

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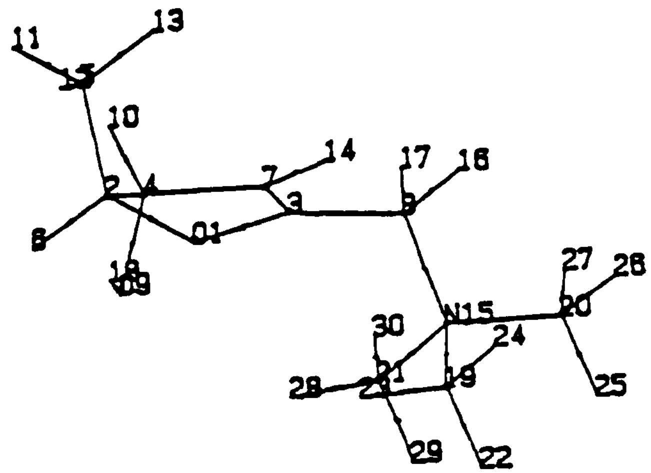

MNDO CHARGES - DEHYDROMUSCARINE (120°) (TRANS)

		x	y	z	charge
1	O	1.4813	-0.0248	-1.4691	-0.2276
2	C	1.4461	-0.5564	-2.7856	0.0628
3	C	0.1916	0.0102	-1.0137	-0.0206
4	C	0.0893	-0.1369	-3.3627	0.1350
5	C	1.6120	-2.0809	-2.7122	0.0063
6	H	2.2978	-0.1094	-3.3524	0.0736
7	C	-0.6397	-0.0889	-2.0597	-0.1230
8	C	-0.1511	0.0016	0.4520	0.1355
9	O	0.1531	1.1605	-3.9074	-0.3066
10	H	-0.3399	-0.8477	-4.1076	0.0528
11	H	1.6134	-2.5267	-3.7334	0.0216
12	H	2.5769	-2.3507	-2.2243	0.0272
13	H	0.7921	-2.5629	-2.1319	-0.0007
14	H	-1.7369	-0.1620	-2.0080	0.0850
15	N	-0.9154	1.2030	0.9358	-0.0864
16	H	-0.7349	-0.9261	0.6559	0.0697
17	H	0.8060	-0.0956	1.0158	0.0822
18	H	0.4566	1.0975	-4.8001	0.1954
19	C	-2.2656	1.3242	0.3039	0.0804
20	C	-1.0979	1.0708	2.4187	0.0814
21	C	-0.1237	2.4422	0.6514	0.0784
22	H	-2.1963	1.5960	-0.7715	0.0697
23	H	-2.8445	0.3779	0.4093	0.0605
24	H	-2.8547	2.1397	0.7832	0.0597
25	H	-1.6897	0.1595	2.6673	0.0609
26	H	-0.1166	0.9974	2.9419	0.0639
27	H	-1.6350	1.9519	2.8397	0.0629
28	H	0.0233	2.5877	-0.4433	0.0767
29	H	-0.6449	3.3460	1.0434	0.0578
30	H	0.8821	2.3931	1.1289	0.0655

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MNDO CHARGES - DEHYDROMUSCARINE (150°) (TRANS)

		x	y	z	charge
1	O	1.5045	-0.0719	-1.4045	-0.2248
2	C	1.5356	-0.6458	-2.7017	0.0625
3	C	0.1954	-0.0549	-0.9992	0.0001
4	C	0.2202	-0.2138	-3.3562	0.1384
5	C	1.6666	-2.1703	-2.5752	0.0060
6	H	2.4250	-0.2305	-3.2335	0.0757
7	C	-0.5762	-0.1238	-2.0934	-0.1427
8	C	-0.1378	0.0297	0.4714	0.1294
9	O	0.3356	1.0688	-3.9260	-0.3039
10	H	-0.1831	-0.9329	-4.1076	0.0493
11	H	1.7167	-2.6454	-3.5819	0.0219
12	H	2.5972	-2.4427	-2.0261	0.0271
13	H	0.8064	-2.6217	-2.0296	-0.0037
14	H	-1.6738	-0.1279	-2.1336	0.0783
15	N	-1.4189	0.7124	0.8666	-0.0831
16	H	-0.0721	-0.9903	0.9161	0.0797
17	H	0.7079	0.6161	0.9003	0.0761
18	H	0.7197	0.9848	-4.7851	0.1943
19	C	-2.6069	-0.1686	0.6357	0.0798
20	C	-1.3503	0.9915	2.3424	0.0804
21	C	-1.5795	2.0199	0.1553	0.0789
22	H	-2.7604	-0.4084	-0.4356	0.0643
23	H	-2.5017	-1.1334	1.1833	0.0618
24	H	-3.5415	0.3245	0.9900	0.0615
25	H	-1.2114	0.0498	2.9225	0.0624
26	H	-0.5038	1.6733	2.5897	0.0661
27	H	-2.2843	1.4794	2.7057	0.0634
28	H	-1.7130	1.8899	-0.9402	0.0734
29	H	-2.4798	2.5631	0.5241	0.0582
30	H	-0.6922	2.6738	0.3195	0.0692

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MNDO CHARGES - DEHYDROMUSCARINE (180°) (TRANS)

		x	y	z	charge
1	O	1.5242	0.0061	-1.3778	-0.2234
2	C	1.5955	-0.5630	-2.6751	0.0613
3	C	0.2091	-0.0238	-0.9923	0.0044
4	C	0.2814	-0.1634	-3.3512	0.1408
5	C	1.7631	-2.0840	-2.5502	0.0066
6	H	2.4835	-0.1230	-3.1891	0.0772
7	C	-0.5400	-0.0951	-2.1025	-0.1477
8	C	-0.1229	0.0765	0.4784	0.1306
9	O	0.3743	1.1215	-3.9193	-0.2999
10	H	-0.0906	-0.8915	-4.1100	0.0461
11	H	1.8445	-2.5546	-3.5569	0.0226
12	H	2.6898	-2.3342	-1.9840	0.0270
13	H	0.9046	-2.5590	-2.0222	-0.0089
14	H	-1.6362	-0.1096	-2.1735	0.0766
15	N	-1.5663	0.0434	0.8981	-0.0826
16	H	0.4203	-0.7652	0.9682	0.0741
17	H	0.3468	1.0204	0.8412	0.0825
18	H	0.7854	1.0518	-4.7668	0.1935
19	C	-2.2235	-1.2432	0.5076	0.0803
20	C	-1.5992	0.1303	2.3994	0.0795
21	C	-2.3191	1.2236	0.3663	0.0787
22	H	-2.2759	-1.3809	-0.5920	0.0656
23	H	-1.6719	-2.1157	0.9274	0.0632
24	H	-3.2704	-1.2847	0.8871	0.0613
25	H	-1.0573	-0.7243	2.8668	0.0637
26	H	-1.1245	1.0716	2.7614	0.0657
27	H	-2.6457	0.1131	2.7827	0.0638
28	H	-2.3787	1.2323	-0.7410	0.0710
29	H	-3.3676	1.2271	0.7435	0.0595
30	H	-1.8390	2.1783	0.6822	0.0669

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		x	y	z	charge
1	O	2.5208	0.0501	5.3531	-0.2407
2	C	3.4877	-0.1416	4.3298	0.0696
3	C	3.0726	0.9422	6.2301	-0.0425
4	C	4.8486	-0.0290	5.0289	0.1311
5	C	3.2249	-1.4681	3.6145	0.0290
6	H	3.3546	0.7035	3.6081	0.0375
7	C	4.4052	0.9230	6.0926	-0.0991
8	C	2.3037	1.7459	7.2412	0.1428
9	O	5.2257	-1.2460	5.6293	-0.3076
10	H	5.6692	0.3563	4.3783	0.0556
11	H	4.0017	-1.6564	2.8383	0.0153
12	H	3.2327	-2.3236	4.3279	0.0192
13	H	2.2305	-1.4597	3.1115	0.0234
14	H	5.1113	1.5139	6.6987	0.0937
15	N	1.8583	0.9407	8.4284	-0.0874
16	H	2.9468	2.5898	7.5844	0.0682
17	H	1.4275	2.2005	6.7232	0.0766
18	H	5.7535	-1.7344	5.0160	0.1963
19	C	3.0453	0.3502	9.1251	0.0791
20	C	1.1349	1.8478	9.3765	0.0819
21	C	0.9326	-0.1580	8.0080	0.0818
22	H	2.7323	-0.2076	10.0377	0.0597
23	H	3.5890	-0.3682	8.4703	0.0764
24	H	3.7609	1.1448	9.4386	0.0567
25	H	0.7880	1.2923	10.2782	0.0626
26	H	1.7956	2.6758	9.7230	0.0593
27	H	0.2404	2.3017	8.8909	0.0621
28	H	0.5468	-0.7118	8.8948	0.0543
29	H	0.0572	0.2484	7.4510	0.0630
30	H	1.4449	-0.9042	7.3604	0.0820

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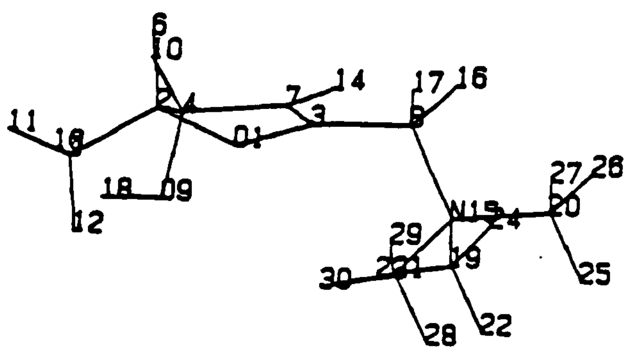

MNDO CHARGE _- EPIALLODEHYDROMUSCARINE(cis)(120°)

		x	y	z	charge
1	O	1.4712	-0.0431	-1.4734	-0.2282
2	C	1.4190	-0.5478	-2.7998	0.0941
3	C	0.1828	0.0023	-1.0135	-0.0108
4	C	0.0688	-0.0937	-3.3652	0.1356
5	C	2.6479	-0.0779	-3.5807	0.0355
6	H	1.4397	-1.6630	-2.7076	0.0346
7	C	-0.6535	-0.0724	-2.0577	-0.1613
8	C	-0.1596	-0.0083	0.4519	0.1348
9	O	0.1406	1.2135	-3.8844	-0.3045
10	H	-0.3476	-0.7953	-4.1267	0.0530
11	H	2.6004	-0.4296	-4.6368	0.0167
12	H	2.7244	1.0334	-3.5887	0.0261
13	H	3.5850	-0.4756	-3.1271	0.0184
14	H	-1.7515	-0.1289	-2.0048	0.0804
15	N	-0.9125	1.2009	0.9366	-0.0869
16	H	-0.7555	-0.9293	0.6511	0.0699
17	H	0.7949	-0.1181	1.0177	0.0832
18	H	-0.4598	1.2925	-4.6087	0.1925
19	C	-2.2546	1.3505	0.2942	0.0820
20	C	-1.1115	1.0591	2.4168	0.0812
21	C	-0.0974	2.4296	0.6720	0.0782
22	H	-2.1712	1.6396	-0.7757	0.0669
23	H	-2.8476	0.4109	0.3801	0.0609
24	H	-2.8369	2.1669	0.7801	0.0594
25	H	-1.6368	1.9460	2.8405	0.0628
26	H	-1.7219	0.1565	2.6515	0.0610
27	H	-0.1367	0.9635	2.9486	0.0644
28	H	0.0679	2.5793	-0.4196	0.0761
29	H	-0.6101	3.3388	1.0624	0.0576
30	H	0.9008	2.3618	1.1630	0.0662

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MNDO CHARGES - EPIALLODEHYDROMUSCARINE (cis)(150°)

		x	y	z	charge
1	O	1.4950	-0.0717	-1.4165	-0.2262
2	C	1.5153	-0.6509	-2.7112	0.0963
3	C	0.1860	-0.0503	-1.0093	0.0081
4	C	0.2084	-0.1966	-3.3679	0.1387
5	C	2.7955	-0.2431	-3.4427	0.0361
6	H	1.5083	-1.7599	-2.5597	0.0309
7	C	-0.5876	-0.1092	-2.1034	-0.1792
8	C	-0.1402	0.0241	0.4638	0.1277
9	O	0.3347	1.0847	-3.9379	-0.3007
10	H	-0.1785	-0.9223	-4.1224	0.0491
11	H	2.8046	-0.6560	-4.4776	0.0158
12	H	2.8915	0.8646	-3.5104	0.0295
13	H	3.6972	-0.6265	-2.9118	0.0177
14	H	-1.6852	-0.1077	-2.1428	0.0732
15	N	-1.4149	0.7112	0.8714	-0.0831
16	H	-0.0803	-1.0006	0.8984	0.0801
17	H	0.7114	0.6002	0.8951	0.0767
18	H	-0.2448	1.1551	-4.6793	0.1910
19	C	-2.6119	-0.1546	0.6300	0.0802
20	C	-1.3407	0.9667	2.3514	0.0803
21	C	-1.5631	2.0305	0.1803	0.0802
22	H	-2.7746	-0.3694	-0.4452	0.0635
23	H	-2.5121	-1.1313	1.1570	0.0626
24	H	-3.5399	0.3395	0.9996	0.0610
25	H	-2.2682	1.4603	2.7236	0.0631
26	H	-1.2126	0.0145	2.9167	0.0629
27	H	-0.4859	1.6345	2.6080	0.0663
28	H	-1.6938	1.9169	-0.9176	0.0701
29	H	-2.4601	2.5753	0.5549	0.0581
30	H	-0.6710	2.6748	0.3562	0.0697

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MNDO CHARGES - EPIALLODEHYDROMUSCARINE (cis)(180°)

		x	y	z	charge
1	O	1.5257	-0.0056	-1.3710	-0.2245
2	C	1.5946	-0.5793	-2.6661	0.0908
3	C	0.2086	-0.0342	-0.9896	0.0115
4	C	0.2898	-0.1626	-3.3497	0.1417
5	C	2.8778	-0.1289	-3.3667	0.0358
6	H	1.6184	-1.6886	-2.5190	0.0269
7	C	-0.5371	-0.1123	-2.1022	-0.1786
8	C	-0.1256	0.0754	0.4803	0.1291
9	O	0.3891	1.1296	-3.9004	-0.2993
10	H	-0.0600	-0.8926	-4.1182	0.0471
11	H	2.9187	-0.5289	-4.4058	0.0138
12	H	2.9454	0.9816	-3.4202	0.0309
13	H	3.7787	-0.4939	-2.8215	0.0179
14	H	-1.6330	-0.1325	-2.1761	0.0718
15	N	-1.5691	0.0443	0.9002	-0.0825
16	H	0.4204	-0.7582	0.9805	0.0751
17	H	0.3407	1.0250	0.8327	0.0820
18	H	-0.0155	1.1430	-4.7526	0.1923
19	C	-2.2146	-1.2562	0.5386	0.0805
20	C	-1.6024	0.1672	2.3991	0.0793
21	C	-2.3320	1.2064	0.3440	0.0798
22	H	-2.2467	-1.4242	-0.5580	0.0652
23	H	-1.6651	-2.1136	0.9911	0.0636
24	H	-3.2666	-1.2922	0.9044	0.0611
25	H	-2.6481	0.1411	2.7842	0.0636
26	H	-1.0457	-0.6662	2.8871	0.0640
27	H	-1.1429	1.1247	2.7376	0.0658
28	H	-2.4139	1.1793	-0.7613	0.0688
29	H	-3.3745	1.2206	0.7377	0.0589
30	H	-1.8489	2.1713	0.6223	0.0674

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MNDO CHARGES - EPIALLODEHYDROMUSCARINE (cis)(240°)

		x	y	z	charge
1	O	1.5448	-0.0336	-1.3467	-0.2345
2	C	1.5971	-0.5314	-2.6736	0.0904
3	C	0.2249	-0.0243	-0.9741	-0.0128
4	C	0.3179	-0.0150	-3.3372	0.1366
5	C	2.9048	-0.0995	-3.3397	0.0361
6	H	1.5692	-1.6475	-2.5933	0.0168
7	C	-0.5152	-0.0014	-2.0929	-0.1363
8	C	-0.1150	0.0124	0.4982	0.1288
9	O	0.4803	1.3018	-3.8088	-0.2938
10	H	-0.0590	-0.6809	-4.1498	0.0461
11	H	2.9353	-0.4381	-4.4008	0.0135
12	H	3.0234	1.0080	-3.3261	0.0341
13	H	3.7840	-0.5374	-2.8132	0.0156
14	H	-1.6103	0.0333	-2.1731	0.0827
15	N	-0.9201	-1.1139	1.0850	-0.0846
16	H	0.8596	0.0857	1.0348	0.0838
17	H	-0.6507	0.9756	0.6671	0.0731
18	H	0.0831	1.3847	-4.6606	0.1934
19	C	-0.1956	-2.4183	0.9735	0.0838
20	C	-1.1026	-0.8188	2.5488	0.0792
21	C	-2.2857	-1.1933	0.4761	0.0811
22	H	-0.0294	-2.7233	-0.0806	0.0641
23	H	0.8026	-2.3635	1.4658	0.0667
24	H	-0.7739	-3.2362	1.4618	0.0586
25	H	-1.6862	-1.6229	3.0540	0.0624
26	H	-0.1217	-0.7389	3.0720	0.0654
27	H	-1.6479	0.1409	2.7038	0.0636
28	H	-2.2634	-1.4630	-0.5990	0.0626
29	H	-2.9011	-1.9712	0.9842	0.0601
30	H	-2.8212	-0.2204	0.5682	0.0631

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MNDO CHARGES - EPIALLODEHYDROMUSCARINE (cis) (270^{0})

		x	y	z	charge
1	O	1.5684	-0.5069	-1.3767	-0.2293
2	C	1.4647	-0.9086	-2.7357	0.0837
3	C	0.2867	-0.2822	-0.9510	-0.0458
4	C	0.2736	-0.1271	-3.3043	0.1374
5	C	2.8000	-0.6793	-3.4463	0.0351
6	H	1.2338	-2.0038	-2.7218	0.0164
7	C	-0.4828	-0.0282	-2.0176	-0.1148
8	C	-0.1236	-0.0777	0.4822	0.1381
9	O	0.6611	1.1609	-3.7200	-0.2952
10	H	-0.2667	-0.6609	-4.1220	0.0486
11	H	2.7197	-0.9393	-4.5268	0.0139
12	H	3.1255	0.3832	-3.3692	0.0337
13	H	3.6030	-1.3093	-2.9988	0.0154
14	H	-1.5403	0.2796	-1.9724	0.0893
15	N	-0.4794	-1.3434	1.2002	-0.0888
16	H	0.7156	0.4424	1.0002	0.0828
17	H	-0.9927	0.6207	0.5095	0.0707
18	H	0.3843	1.3065	-4.6104	0.1954
19	C	0.6820	-2.2870	1.2000	0.0843
20	C	-0.8387	-1.0103	2.6162	0.0825
21	C	-1.6525	-1.9947	0.5365	0.0827
22	H	0.9552	-2.5992	0.1665	0.0694
23	H	1.5774	-1.8185	1.6697	0.0681
24	H	0.4406	-3.2129	1.7712	0.0558
25	H	-1.1206	-1.9269	3.1841	0.0618
26	H	0.0180	-0.5320	3.1447	0.0649
27	H	-1.7035	-0.3083	2.6559	0.0610
28	H	-1.4139	-2.2944	-0.5094	0.0622
29	H	-1.9583	-2.9157	1.0844	0.0608
30	H	-2.5295	-1.3076	0.5089	0.0597

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MNDO CHARGES - MUSCARONE (cis)(150^{o})

		x	y	z	charge
1	O	1.6270	-0.0240	-1.1443	-0.2920
2	C	1.9041	-0.4851	-2.4574	0.0681
3	C	0.2148	-0.0288	-0.9837	0.0996
4	C	0.7975	-1.4621	-2.7864	0.2004
5	C	3.3116	-1.0783	-2.5162	0.0365
6	H	1.8107	0.3911	-3.1430	0.0453
7	C	-0.2728	-1.2794	-1.7319	-0.1021
8	C	-0.1237	0.0310	0.5225	0.0608
9	H	-0.1312	0.8895	-1.5126	0.0187
10	O	0.7698	-2.2748	-3.6767	-0.2010
11	H	3.5576	-1.4259	-3.5460	0.0324
12	H	4.0747	-0.3222	-2.2200	0.0255
13	H	3.4043	-1.9482	-1.8262	0.0139
14	H	-0.2747	-2.1841	-1.0815	0.0579
15	H	-1.2732	-1.1472	-2.2042	0.0554
16	N	-1.4089	0.7014	0.9336	-0.0868
17	H	-0.0963	-1.0087	0.9236	0.0705
18	H	0.7130	0.5653	1.0313	0.0811
19	C	-2.5879	0.0508	0.2808	0.0803
20	C	-1.5555	0.5682	2.4233	0.0829
21	C	-1.3973	2.1626	0.5967	0.0816
22	H	-2.5639	0.1939	-0.8223	0.0590
23	H	-2.6073	-1.0429	0.4935	0.0636
24	H	-3.5432	0.4923	0.6473	0.0638
25	H	-0.7017	1.0481	2.9554	0.0660
26	H	-2.4931	1.0525	2.7819	0.0634
27	H	-1.5930	-0.5029	2.7290	0.0633
28	H	-1.3600	2.3361	-0.5014	0.0630
29	H	-2.3197	2.6642	0.9704	0.0615
30	H	-0.5204	2.6722	1.0581	0.0676

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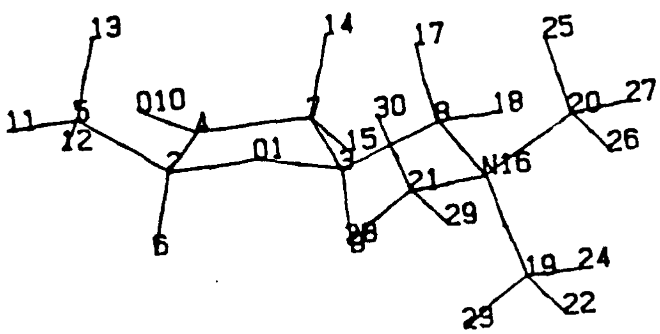

AD-A191 712 MOLECULAR MODELING IN DRUG DESIGN FOR THE DEVELOPMENT OF ORGANOPHOSPHORUS ANTIDOTES/PROPHYLACTICS(U) NEW JERSEY INST OF TECH NEWARK T GUND AUG 85 2/2

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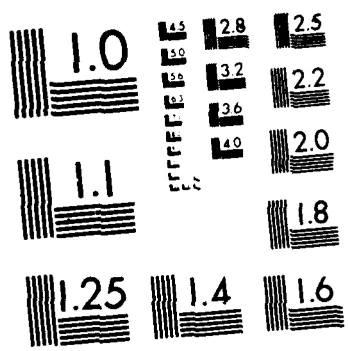

MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS 1963 A

MNDO CHARGES - MUSCARONE (cis)(180^{O})

		x	y	z	charge
1	O	1.6212	-0.0648	-1.1108	-0.2936
2	C	1.9370	-0.4346	-2.4430	0.0699
3	C	0.2031	-0.0214	-0.9975	0.1009
4	C	0.8298	-1.3719	-2.8631	0.2024
5	C	3.3394	-1.0396	-2.4996	0.0372
6	H	1.8726	0.4872	-3.0696	0.0467
7	C	-0.2748	-1.2115	-1.8413	-0.1084
8	C	-0.1484	-0.0261	0.5068	0.0604
9	H	-0.1106	0.9417	-1.4685	0.0290
10	O	0.8228	-2.1513	-3.7830	-0.2012
11	H	3.6106	-1.3263	-3.5417	0.0323
12	H	4.1012	-0.3118	-2.1365	0.0265
13	H	3.4042	-1.9514	-1.8624	0.0133
14	H	-0.3159	-2.1509	-1.2432	0.0501
15	H	-1.2446	-1.0169	-2.3549	0.0552
16	N	-1.5919	0.0177	0.9399	-0.0861
17	H	0.3309	-0.9267	0.9581	0.0745
18	H	0.3787	0.8538	0.9471	0.0772
19	C	-2.3465	-1.2241	0.5779	0.0806
20	C	-1.6216	0.1461	2.4383	0.0822
21	C	-2.2836	1.2070	0.3481	0.0801
22	H	-2.4823	-1.3187	-0.5199	0.0612
23	H	-1.8261	-2.1339	0.9561	0.0657
24	H	-3.3717	-1.2098	1.0147	0.0621
25	H	-1.1011	1.0722	2.7754	0.0649
26	H	-2.6674	0.1963	2.8203	0.0631
27	H	-1.1238	-0.7248	2.9243	0.0651
28	H	-2.3345	1.1303	-0.7616	0.0596
29	H	-3.3300	1.2892	0.7228	0.0632
30	H	-1.7491	2.1497	0.6076	0.0658

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MNDO CHARGES - MUSCARONE (cis)(210°)

		x	y	z	charge
1	O	1.6434	-0.0273	-1.0909	-0.2957
2	C	1.9673	-0.4340	-2.4104	0.0696
3	C	0.2249	-0.0243	-0.9741	0.0992
4	C	0.8890	-1.4198	-2.7930	0.2033
5	C	3.3879	-0.9964	-2.4506	0.0372
6	H	1.8724	0.4626	-3.0688	0.0493
7	C	-0.2175	-1.2580	-1.7736	-0.1169
8	C	-0.1225	0.0133	0.5308	0.0606
9	H	-0.1201	0.9112	-1.4777	0.0435
10	O	0.9042	-2.2312	-3.6848	-0.2010
11	H	3.6653	-1.3112	-3.4829	0.0326
12	H	4.1273	-0.2327	-2.1162	0.0279
13	H	3.4829	-1.8826	-1.7818	0.0110
14	H	-0.2275	-2.1764	-1.1425	0.0415
15	H	-1.1943	-1.1122	-2.2902	0.0590
16	N	-1.3963	-0.6260	1.0226	-0.0857
17	H	0.7367	-0.4361	1.0823	0.0834
18	H	-0.1372	1.0926	0.8147	0.0699
19	C	-1.3931	-2.1167	0.8789	0.0735
20	C	-1.5361	-0.3118	2.4869	0.0820
21	C	-2.5815	-0.0622	0.3012	0.0795
22	H	-1.4254	-2.4281	-0.1863	0.0673
23	H	-0.4916	-2.5635	1.3575	0.0674
24	H	-2.2933	-2.5658	1.3583	0.0619
25	H	-1.5769	0.7881	2.6626	0.0638
26	H	-2.4707	-0.7492	2.9081	0.0631
27	H	-0.6774	-0.7214	3.0677	0.0657
28	H	-2.5499	-0.3167	-0.7824	0.0591
29	H	-3.5327	-0.4739	0.7106	0.0636
30	H	-2.6163	1.0475	0.3971	0.0644

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MNDO CHARGES - MUSCARONE (trans) (90^{o})

		x	y	z	charge
1	O	1.6307	-0.0252	-1.1581	-0.3058
2	C	1.8937	0.1957	-2.5371	0.0631
3	C	0.2223	-0.0280	-0.9738	0.0918
4	C	0.5980	0.6613	-3.1676	0.1990
5	C	2.4739	-1.0703	-3.1696	0.0226
6	H	2.6259	1.0360	-2.5835	0.0633
7	C	-0.3605	0.9192	-2.0254	-0.0979
8	C	-0.1187	0.0189	0.5372	0.0733
9	H	-0.0607	-1.0586	-1.3077	0.0417
10	O	0.3400	0.7674	-4.3405	-0.1954
11	H	2.7310	-0.9014	-4.2406	0.0332
12	H	3.4028	-1.3881	-2.6424	0.0281
13	H	1.7460	-1.9123	-3.1188	0.0076
14	H	-1.4121	0.6734	-2.3037	0.0693
15	H	-0.2552	1.9971	-1.7788	0.0383
16	N	-0.6195	1.2707	1.2082	-0.0861
17	H	-0.8952	-0.7642	0.7121	0.0573
18	H	0.7818	-0.3491	1.0838	0.0849
19	C	0.3900	2.3708	1.0911	0.0820
20	C	-0.7948	0.9712	2.6743	0.0801
21	C	-1.9517	1.7146	0.6870	0.0814
22	H	0.5698	2.6580	0.0338	0.0607
23	H	0.0507	3.2849	1.6308	0.0599
24	H	1.3697	2.0593	1.5213	0.0690
25	H	-1.5415	0.1592	2.8341	0.0629
26	H	0.1646	0.6487	3.1411	0.0655
27	H	-1.1494	1.8691	3.2315	0.0633
28	H	-1.9052	2.0421	-0.3709	0.0613
29	H	-2.7023	0.8943	0.7594	0.0632
30	H	-2.3365	2.5848	1.2670	0.0624

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MNDO CHARGES - MUSCARONE (trans)(120^{o})

		x	y	z	charge
1	O	1.6310	-0.0256	-1.1543	-0.3048
2	C	1.9017	0.2004	-2.5307	0.0634
3	C	0.2217	-0.0292	-0.9743	0.0937
4	C	0.6108	0.6712	-3.1658	0.1995
5	C	2.4822	-1.0644	-3.1653	0.0225
6	H	2.6362	1.0391	-2.5699	0.0640
7	C	-0.3575	0.9168	-2.0292	-0.0987
8	C	-0.1188	0.0197	0.5378	0.0725
9	H	-0.0601	-1.0593	-1.3109	0.0405
10	O	0.3616	0.7888	-4.3395	-0.1960
11	H	2.7448	-0.8920	-4.2344	0.0331
12	H	3.4078	-1.3864	-2.6349	0.0283
13	H	1.7522	-1.9050	-3.1213	0.0073
14	H	-1.4030	0.6613	-2.3215	0.0681
15	H	-0.2670	1.9947	-1.7772	0.0390
16	N	-0.7238	1.2337	1.1929	-0.0859
17	H	-0.8256	-0.8236	0.7273	0.0570
18	H	0.8075	-0.2634	1.0917	0.0852
19	C	0.2091	2.4024	1.1057	0.0815
20	C	-0.9180	0.9217	2.6542	0.0801
21	C	-2.0677	1.5849	0.6335	0.0813
22	H	0.4025	2.7032	0.0550	0.0608
23	H	-0.2105	3.2899	1.6331	0.0603
24	H	1.1943	2.1609	1.5671	0.0683
25	H	-1.6148	0.0633	2.7952	0.0631
26	H	0.0477	0.6614	3.1462	0.0656
27	H	-1.3450	1.7939	3.2014	0.0633
28	H	-2.0099	1.9281	-0.4191	0.0612
29	H	-2.7579	0.7111	0.6746	0.0635
30	H	-2.5330	2.4187	1.2079	0.0623

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MNDO CHARGES - F2268 (cis)(150^{o})

		x	y	z	charge
1	O	1.6221	-0.0270	-1.1486	-0.3052
2	C	1.8433	-0.5907	-2.4278	0.2367
3	C	0.2202	-0.0347	-0.9772	0.0598
4	O	0.7339	-1.3999	-2.7703	-0.2959
5	C	3.1244	-1.4234	-2.4191	0.0171
6	H	1.8877	0.2437	-3.1676	0.0428
7	C	-0.1722	-1.3232	-1.6931	0.1166
8	C	-0.1186	0.0338	0.5236	0.0634
9	H	-0.1485	0.8553	-1.5378	0.0325
10	H	4.0051	-0.7947	-2.1532	0.0248
11	H	3.0542	-2.2511	-1.6763	0.0142
12	H	3.3128	-1.8735	-3.4208	0.0346
13	H	-0.0004	-2.2314	-1.0701	0.0283
14	H	-1.2057	-1.3251	-2.1077	0.0439
15	N	-1.4084	0.7048	0.9175	-0.0873
16	H	-0.0938	-1.0027	0.9332	0.0719
17	H	0.7144	0.5738	1.0326	0.0830
18	C	-2.5744	0.0439	0.2525	0.0783
19	C	-1.5706	0.5835	2.4056	0.0829
20	C	-1.3941	2.1622	0.5660	0.0808
21	H	-2.5321	0.1715	-0.8522	0.0603
22	H	-2.5957	-1.0471	0.4789	0.0636
23	H	-3.5363	0.4879	0.5980	0.0650
24	H	-0.7241	1.0704	2.9428	0.0663
25	H	-2.5137	1.0678	2.7493	0.0639
26	H	-1.6086	-0.4852	2.7198	0.0635
27	H	-1.3449	2.3266	-0.5329	0.0641
28	H	-2.3211	2.6661	0.9248	0.0620
29	H	-0.5233	2.6775	1.0327	0.0679

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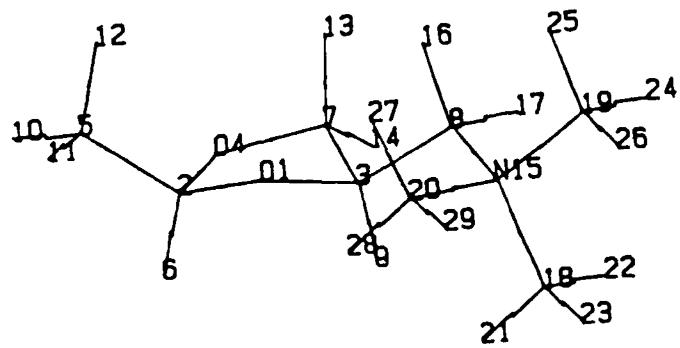

MNDO CHARGES - F2268 (cis)(180^{o})

		x	y	z	charge
1	O	1.6102	-0.0745	-1.1166	-0.3049
2	C	1.8629	-0.5355	-2.4278	0.2391
3	C	0.2020	-0.0278	-0.9980	0.0621
4	O	0.7983	-1.3842	-2.8036	-0.2946
5	C	3.1891	-1.2922	-2.4756	0.0221
6	H	1.8524	0.3449	-3.1143	0.0370
7	C	-0.2047	-1.2460	-1.8219	0.1137
8	C	-0.1473	-0.0290	0.5023	0.0626
9	H	-0.1218	0.9200	-1.4920	0.0406
10	H	4.0346	-0.6305	-2.1774	0.0252
11	H	3.1727	-2.1651	-1.7833	0.0163
12	H	3.3941	-1.6702	-3.5036	0.0342
13	H	-0.1840	-2.1871	-1.2253	0.0211
14	H	-1.1743	-1.1255	-2.3569	0.0399
15	N	-1.5930	0.0184	0.9253	-0.0869
16	H	0.3310	-0.9265	0.9608	0.0772
17	H	0.3766	0.8537	0.9406	0.0784
18	C	-2.3396	-1.2222	0.5460	0.0787
19	C	-1.6352	0.1405	2.4228	0.0825
20	C	-2.2766	1.2098	0.3292	0.0792
21	H	-2.4539	-1.3133	-0.5547	0.0608
22	H	-1.8249	-2.1331	0.9294	0.0669
23	H	-3.3720	-1.2101	0.9654	0.0634
24	H	-1.1168	1.0649	2.7678	0.0654
25	H	-2.6845	0.1895	2.7953	0.0637
26	H	-1.1425	-0.7328	2.9097	0.0655
27	H	-2.3211	1.1353	-0.7809	0.0605
28	H	-3.3254	1.2937	0.6964	0.0638
29	H	-1.7423	2.1510	0.5946	0.0665

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MNDO CHARGES - F2268 (trans)(120°)

		x	y	z	charge
1	O	1.6065	-0.0121	-1.1843	-0.3173
2	C	1.8061	0.4267	-2.5158	0.2349
3	C	0.2072	-0.0552	-0.9780	0.0570
4	O	0.5441	0.6175	-3.1247	-0.2880
5	C	2.6202	-0.6023	-3.2983	0.0191
6	H	2.3159	1.4183	-2.4647	0.0355
7	C	-0.3458	0.8631	-2.0600	0.1154
8	C	-0.0989	0.0547	0.5349	0.0693
9	H	-0.0617	-1.0940	-1.2954	0.0566
10	H	3.6161	-0.7638	-2.8253	0.0261
11	H	2.0919	-1.5828	-3.3335	0.0180
12	H	2.7881	-0.2626	-4.3462	0.0328
13	H	-1.3683	0.5923	-2.4111	0.0604
14	H	-0.2720	1.9508	-1.8467	0.0079
15	N	-0.9235	1.1684	1.1256	-0.0861
16	H	-0.6071	-0.9002	0.8111	0.0597
17	H	0.8738	0.0112	1.0795	0.0860
18	C	-0.2024	2.4782	1.0305	0.0791
19	C	-1.1183	0.8735	2.5897	0.0806
20	C	-2.2786	1.2658	0.4997	0.0799
21	H	-0.0253	2.7864	-0.0198	0.0623
22	H	-0.7884	3.2925	1.5155	0.0615
23	H	0.7911	2.4250	1.5323	0.0678
24	H	-1.6731	-0.0815	2.7403	0.0638
25	H	-0.1415	0.7886	3.1200	0.0662
26	H	-1.7020	1.6798	3.0912	0.0637
27	H	-2.2254	1.5970	-0.5576	0.0595
28	H	-2.8046	0.2841	0.5333	0.0648
29	H	-2.9100	2.0152	1.0303	0.0635

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MNDO CHARGES - F2268 (trans)(150^{o})

		x	y	z	charge
1	O	1.6321	-0.0136	-1.1356	-0.3165
2	C	1.8951	0.4341	-2.4530	0.2358
3	C	0.2233	-0.0273	-0.9766	0.0651
4	O	0.6867	0.9202	-3.0014	-0.2895
5	C	2.4422	-0.7072	-3.3092	0.0119
6	H	2.6099	1.2876	-2.3779	0.0521
7	C	-0.1466	1.1388	-1.8875	0.1053
8	C	-0.1003	0.0280	0.5317	0.0622
9	H	-0.1538	-0.9818	-1.4198	0.0537
10	H	3.3904	-1.1051	-2.8801	0.0275
11	H	1.7123	-1.5469	-3.3700	0.0113
12	H	2.6537	-0.3588	-4.3462	0.0341
13	H	-1.2005	1.1363	-2.2475	0.0501
14	H	0.1514	2.1297	-1.4728	0.0167
15	N	-1.3664	0.6648	1.0466	-0.0860
16	H	-0.0332	-1.0201	0.9095	0.0759
17	H	0.7473	0.5677	1.0160	0.0757
18	C	-1.4508	2.1386	0.7980	0.0808
19	C	-1.4076	0.4592	2.5368	0.0816
20	C	-2.5549	-0.0183	0.4445	0.0768
21	H	-1.6361	2.3745	-0.2699	0.0614
22	H	-2.3117	2.5853	1.3467	0.0616
23	H	-0.5241	2.6572	1.1353	0.0690
24	H	-1.3747	-0.6235	2.7994	0.0645
25	H	-0.5450	0.9602	3.0343	0.0664
26	H	-2.3426	0.8752	2.9784	0.0635
27	H	-2.5745	0.1080	-0.6608	0.0598
28	H	-2.5384	-1.1115	0.6597	0.0650
29	H	-3.5052	0.3995	0.8499	0.0642

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MNDO CHARGES - F2268 (trans)(180^{O})

		x	y	z	charge
1	O	1.6365	-0.0770	-1.1255	-0.3103
2	C	1.9091	0.4770	-2.3985	0.2360
3	C	0.2294	-0.0916	-0.9728	0.0623
4	O	0.7001	0.9402	-2.9639	-0.2900
5	C	2.5434	-0.5739	-3.3090	0.0135
6	H	2.5741	1.3588	-2.2406	0.0499
7	C	-0.2055	1.0435	-1.8912	0.1105
8	C	-0.0884	0.0238	0.5294	0.0597
9	H	-0.1051	-1.0748	-1.3831	0.0435
10	H	3.4966	-0.9529	-2.8738	0.0271
11	H	1.8600	-1.4425	-3.4510	0.0110
12	H	2.7700	-0.1455	-4.3124	0.0341
13	H	-1.2272	0.9225	-2.3170	0.0484
14	H	-0.0672	2.0500	-1.4309	0.0213
15	N	-1.5251	0.0313	0.9844	-0.0866
16	H	0.4290	-0.8380	1.0146	0.0785
17	H	0.4160	0.9404	0.9164	0.0753
18	C	-2.2411	1.2839	0.5839	0.0788
19	C	-1.5380	-0.0416	2.4857	0.0824
20	C	-2.2571	-1.1565	0.4416	0.0795
21	H	-2.3709	1.3529	-0.5160	0.0602
22	H	-3.2658	1.3143	1.0208	0.0635
23	H	-1.6926	2.1887	0.9332	0.0660
24	H	-1.0445	-0.9722	2.8499	0.0655
25	H	-1.0046	0.8288	2.9332	0.0652
26	H	-2.5798	-0.0422	2.8819	0.0635
27	H	-2.3277	-1.1131	-0.6688	0.0609
28	H	-1.7429	-2.1043	0.7227	0.0669
29	H	-3.2983	-1.1986	0.8365	0.0634

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MNDO CHARGES - F2268 (trans)(210^{o})

		x	y	z	charge
1	O	1.6348	-0.0274	-1.0985	-0.3149
2	C	1.9428	0.5914	-2.3329	0.2361
3	C	0.2249	-0.0243	-0.9741	0.0638
4	O	0.7539	1.1079	-2.8947	-0.2920
5	C	2.5770	-0.4187	-3.2885	0.0136
6	H	2.6198	1.4506	-2.1130	0.0507
7	C	-0.1714	1.1681	-1.8356	0.1171
8	C	-0.1214	0.0131	0.5259	0.0588
9	H	-0.1184	-0.9768	-1.4452	0.0330
10	H	3.5144	-0.8390	-2.8569	0.0257
11	H	1.8816	-1.2652	-3.4921	0.0088
12	H	2.8314	0.0606	-4.2617	0.0348
13	H	-1.1862	1.0900	-2.2871	0.0517
14	H	-0.0249	2.1446	-1.3171	0.0283
15	N	-1.3945	-0.6327	1.0088	-0.0855
16	H	0.7382	-0.4728	1.0464	0.0852
17	H	-0.1130	1.0798	0.8524	0.0680
18	C	-2.6143	0.1080	0.5557	0.0799
19	C	-1.3830	-0.6169	2.5118	0.0824
20	C	-1.4740	-2.0543	0.5461	0.0794
21	H	-2.7529	0.0444	-0.5435	0.0606
22	H	-3.5351	-0.3241	1.0111	0.0633
23	H	-2.5613	1.1829	0.8443	0.0643
24	H	-0.5111	-1.1815	2.9157	0.0660
25	H	-1.3277	0.4262	2.9007	0.0640
26	H	-2.3038	-1.0868	2.9285	0.0635
27	H	-1.5481	-2.1130	-0.5634	0.0625
28	H	-0.5751	-2.6291	0.8676	0.0684
29	H	-2.3747	-2.5604	0.9637	0.0625

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T MEF72N.OUT MNDO CHARGES - 5-METHYLFURMETHIDE (GLOBAL MIN.)

		x	y	z	charge
1	O	3.5875	0.9616	4.0754	-0.0961
2	C	4.5846	0.4381	3.3054	0.0401
3	C	3.8983	0.6294	5.3626	-0.1803
4	C	5.4695	-0.1779	4.0996	-0.1383
5	C	4.6535	0.5533	1.8135	0.0818
6	C	5.0483	-0.0589	5.3613	-0.0260
7	C	3.0847	0.9875	6.5740	0.1643
8	H	6.3857	-0.6954	3.7711	0.1160
9	H	3.7539	0.0835	1.3557	0.0211
10	H	4.6827	1.6261	1.5171	0.0301
11	H	5.5583	0.0514	1.4017	0.0355
12	H	5.5599	-0.4639	6.2498	0.0968
13	N	1.8038	0.2119	6.6928	-0.0914
14	H	2.8776	2.0824	6.5405	0.0717
15	H	3.7106	0.8075	7.4792	0.0682
16	C	2.0891	-1.2579	6.7128	0.0858
17	C	0.8807	0.5267	5.5570	0.0845
18	C	1.1321	0.5955	7.9774	0.0816
19	H	1.1510	-1.8430	6.8522	0.0579
20	H	2.5520	-1.5962	5.7579	0.0655
21	H	2.7829	-1.5185	7.5451	0.0582
22	H	0.6757	1.6206	5.4997	0.0632
23	H	1.3026	0.1982	4.5812	0.0716
24	H	-0.0944	0.0016	5.6810	0.0547
25	H	0.9038	1.6862	7.9983	0.0623
26	H	0.1729	0.0437	8.1097	0.0610
27	H	1.7788	0.3628	8.8547	0.0601

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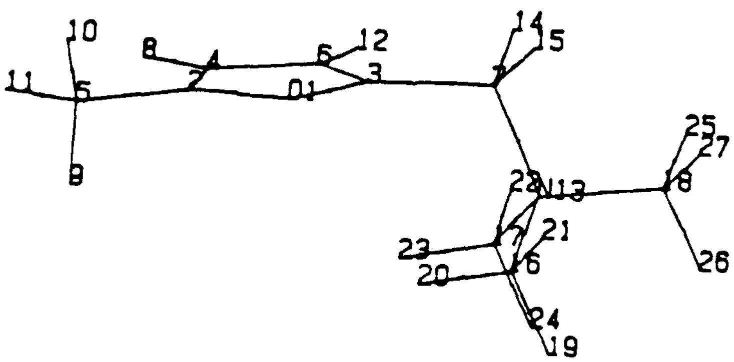


CHARGES FROM MINDO

5-Methylfurmethide (GLOBAL MINIMUM WITH 72.3^{o} DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	O	-0.0961	1.01[illegible]2
2	C	0.0401	
3	C	-0.1803	
4	C	-0.1383	
5	C	0.0818	
6	C	-0.0260	
7	C	0.1643	
8	H	0.1160	
9	H	0.0211	
10	H	0.0301	
11	H	0.0355	
12	H	0.0968	
13	N	-0.0914	
14	H	0.0717	
15	H	0.0682	
16	C	0.0858	
17	C	0.0845	
18	C	0.0816	
19	H	0.0579	
20	H	0.0655	
21	H	0.0582	
22	H	0.0632	
23	H	0.0716	
24	H	0.0547	
25	H	0.0623	
26	H	0.0610	
27	H	0.0601	

CHARGES FROM MINDO

5-Methylfurmethide (LOCAL MINIMUM WITH 120° DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	O	-0.0796	1.0188
2	C	0.0452	
3	C	-0.1707	
4	C	-0.1404	
5	C	0.0814	
6	C	-0.0446	
7	C	0.1585	
8	H	0.1144	
9	H	0.0338	
10	H	0.0244	
11	H	0.0306	
12	H	0.0867	
13	N	-0.0880	
14	H	0.0676	
15	H	0.0743	
16	C	0.0817	
17	C	0.0834	
18	C	0.0844	
19	H	0.0629	
20	H	0.0612	
21	H	0.0618	
22	H	0.0670	
23	H	0.0570	
24	H	0.0632	
25	H	0.0643	
26	H	0.0620	
27	H	0.0575	

CHARGES FROM MNDO

5-Methylfurmethide (LOCAL MINIMUM WITH 150° DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	O	-0.0803	1.0237
2	C	0.0428	
3	C	-0.1470	
4	C	-0.1386	
5	C	0.0833	
6	C	-0.0635	
7	C	0.1552	
8	H	0.1127	
9	H	0.0328	
10	H	0.0257	
11	H	0.0288	
12	H	0.0796	
13	N	-0.0827	
14	H	0.0754	
15	H	0.0633	
16	C	0.0808	
17	C	0.0840	
18	C	0.0812	
19	H	0.0643	
20	H	0.0622	
21	H	0.0632	
22	H	0.0670	
23	H	0.0576	
24	H	0.0652	
25	H	0.0648	
26	H	0.0631	
27	H	0.0591	

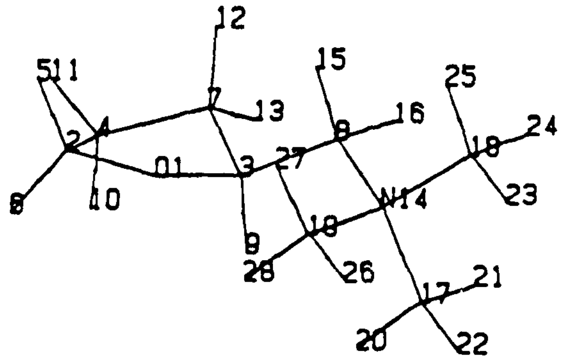
CHARGES FROM MNDO

TFTM (GLOBAL MINIMUM WITH 71.38° DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE
1	O	-0.3421
2	C	0.1404
3	C	0.0924
4	C	-0.0513
5	H	0.0285
6	H	0.0419
7	C	-0.0428
8	C	0.0663
9	H	0.0256
10	H	0.0357
11	H	0.0590
12	H	0.0357
13	H	0.0481
14	N	-0.0834
15	H	0.0723
16	H	0.0598
17	C	0.0819
18	C	0.0825
19	C	0.0864
20	H	0.0641
21	H	0.0583
22	H	0.0605
23	H	0.0618
24	H	0.0590
25	H	0.0630
26	H	0.0508
27	H	0.0676
28	H	0.0779

CATIONIC HEAD CHARGE

0.9288



CHARGES FROM MNDO

TFTM (LOCAL MINIMUM WITH 150° DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	O	-0.3128	0.9287
2	C	0.1384	
3	C	0.0990	
4	C	-0.0507	
5	H	0.0334	
6	H	0.0425	
7	C	-0.0556	
8	C	0.0567	
9	H	0.0180	
10	H	0.0330	
11	H	0.0572	
12	H	0.0372	
13	H	0.0316	
14	N	-0.0857	
15	H	0.0673	
16	H	0.0805	
17	C	0.0811	
18	C	0.0834	
19	C	0.0819	
20	H	0.0628	
21	H	0.0611	
22	H	0.0599	
23	H	0.0616	
24	H	0.0623	
25	H	0.0655	
26	H	0.0640	
27	H	0.0591	
28	H	0.0672	

CHARGES FROM MNDO

TFTM (LOCAL MINIMUM WITH 180° DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	O	-0.3130	0.9240
2	C	0.1400	
3	C	0.1003	
4	C	-0.0498	
5	H	0.0252	
6	H	0.0495	
7	C	-0.0594	
8	C	0.0538	
9	H	0.0285	
10	H	0.0375	
11	H	0.0568	
12	H	0.0288	
13	H	0.0315	
14	N	-0.0845	
15	H	0.0721	
16	H	0.0754	
17	C	0.0809	
18	C	0.0827	
19	C	0.0813	
20	H	0.0646	
21	H	0.0597	
22	H	0.0613	
23	H	0.0612	
24	H	0.0643	
25	H	0.0646	
26	H	0.0601	
27	H	0.0607	
28	H	0.0658	

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